OMB No. 0990-0115
PHS 2008-1

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

SOLICITATION OF

THE NATIONAL INSTITUTES OF HEALTH AND

THE CENTERS FOR DISEASE CONTROL

AND PREVENTION

FOR

SMALL BUSINESS INNOVATION RESEARCH CONTRACT PROPOSALS

PROPOSAL RECEIPT DATE

NOVEMBER 5, 2007

Internet: http://grants.nih.gov/grants/funding/sbir.htm

TABLE OF CONTENTS

APPENDIX A — PROPOSAL COVER SHEET (MS Word | PDF) - USE FOR PHASE I PROPOSALS

APPENDIX B — ABSTRACT OF RESEARCH PLAN (MS Word | PDF) - USE FOR PHASE I, PHASE II, AND FAST-TRACK PROPOSALS

APPENDIX C — PRICING PROPOSAL (MS Word | PDF) - USE FOR PHASE I, PHASE II AND FAST-TRACK PROPOSALS

APPENDIX D — PHASE II TECHNICAL PROPOSAL COVER SHEET (MS Word | PDF) - USE FOR PHASE II AND FAST-TRACK PROPOSALS

APPENDIX E — STATEMENT OF WORK SAMPLE FORMAT (MS Word | PDF) - USE FOR PHASE II AND FAST-TRACK PROPOSALS

APPENDIX F — SUMMARY OF RELATED ACTIVITIES (MS Word | PDF) - USE FOR PHASE II AND FAST-TRACK PROPOSALS

APPENDIX G — PROPOSAL SUMMARY AND DATA RECORD (MS Word | PDF) - USE FOR PHASE II AND FAST-TRACK PROPOSALS

The Appendices noted above are in Microsoft Word and Adobe Acrobat Reader fillable format.

NOTE: Other software packages for completing these proposals may be available from other sources; however, it is essential that the type size and format specifications are met or the proposal may be returned without review.

DISCLAIMER: Reference to these software packages neither constitutes nor should be inferred to be an endorsement or recommendation of any product, service, or enterprise by the National Institutes of Health, any other agency of the United States Government, or any employee of the United States Government. No warranties are stated or implied.

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

SOLICITATION OF THE NATIONAL INSTITUTES OF HEALTH AND THE CENTERS FOR DISEASE CONTROL AND PREVENTION FOR SMALL BUSINESS INNOVATION RESEARCH CONTRACT PROPOSALS

I. PROGRAM DESCRIPTION

A. PURPOSE OF SOLICITATION

The National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) invite small business concerns to submit research proposals under this Small Business Innovation Research (SBIR) Contract Solicitation. Firms with the capability to conduct research and development (R&D) in any of the health related topic areas described in Section XII, and to commercialize the results of that R&D, are encouraged to participate.

This solicitation is for Phase I contract proposals and also for Phase I/Phase II Fast-Track contract proposals (see specific topics listed in Section XII and awarding components identified as accepting Fast-Track proposals).

Included are instructions for offerors to prepare contract proposals, a description of the proposal review process, and some conditions of a contract award. **Contract proposals will be accepted only if they respond specifically to a research topic within this solicitation (see Section XII "Research Topics").** Otherwise, proposals will be returned to the offeror(s) without evaluation.

To apply for an SBIR GRANT rather than an SBIR CONTRACT, use the Omnibus Solicitation of the NIH, CDC, and FDA for Small Business Innovation Research Applications (http://grants.nih.gov/grants/guide/pa-files/PA-07-280.html).

The objectives of the SBIR program include stimulating technological innovation in the private sector, strengthening the role of small business in meeting Federal R/R&D needs, increasing private sector commercialization of innovations developed through Federal SBIR R&D, increasing small business participation in Federal R&D, and fostering and encouraging participation by socially and economically disadvantaged small business concerns and women-owned small business concerns in the SBIR program.

The Federal SBIR program is authorized under Public Laws 97-219, 99-443, 102-564, and 106-554. The basic design of the NIH/CDC SBIR program is in accordance with the Small Business Administration (SBA) SBIR Program Policy Directive, 2002. This SBIR Contract solicitation strives to encourage scientific and technical innovation in areas specifically identified by the NIH/CDC awarding components shown in Section I.C. The guidelines presented in this solicitation reflect the flexibility provided in the Policy Directive to encourage proposals based on scientific and technical approaches most likely to yield results important to the NIH/CDC and to the private sector.

B. THREE PHASE PROGRAM

The SBIR program consists of three separate phases:

Phase I: Feasibility
$100,000
6 months

The objective of Phase I is to determine the scientific or technical feasibility and commercial merit of the proposed research or R&D efforts and the quality of performance of the small business concern, prior to providing further Federal support in Phase II. Phase I awards normally may not exceed $100,000 for direct costs, indirect costs, and profit (fixed fee) for a period normally not to exceed 6 months.

Phase II: Full R/R&D Effort
$750,000
2 years

The objective of Phase II is to continue the research or R&D efforts initiated in Phase I. Funding shall be based on the results of Phase I and the scientific and technical merit and commercial potential of the Phase II proposal. Phase II awards normally may not exceed $750,000 for direct costs, indirect costs, and profit (fixed fee) for a period normally not to exceed two years. *Phase II proposals may only be submitted upon the request of the Contracting Officer, if not submitted concurrently with the initial*

Phase I proposal under the Fast-Track procedure (described in Section V). Only one Phase II award may result from a single Phase I SBIR contract.

Phase III: Commercialization stage without SBIR funds

The objective of Phase III, where appropriate, is for the small business concern to pursue with non-SBIR funds the commercialization objectives resulting from the outcomes of the research or R&D funded in Phases I and II. Phase III may involve follow-on, non-SBIR funded R&D or production contracts for products or processes intended for use by the U.S. Government.

The competition for SBIR Phase I and Phase II awards satisfies any competition requirement of the Armed Services Procurement Act, the Federal Property and Administrative Services Act, and the competition in Contracting Act. Therefore, an agency that wishes to fund an SBIR Phase III project is not required to conduct another competition in order to satisfy those statutory provisions. As a result, in conducting actions relative to a Phase III SBIR award, it is sufficient to state for purposes of a Justification and Approval pursuant to FAR 6.302-5 that the project is a SBIR Phase III award that is derived from, extends, or logically concludes efforts performed under prior SBIR funding agreements and is authorized under 10 U.S.C. 2304(b)(2) or 41 U.S.C. 253(b)(2).

The NIH is interested in developing products and services via the SBIR program that improve the health of the American people. In its commitment to also support President Bush's Executive Order 13329, encouraging innovation in manufacturing-related research and development, NIH seeks, through the SBIR program, biomedical research related to advanced processing, manufacturing processes, equipment and systems; or manufacturing workforce skills and protection. This solicitation includes some topic areas that are considered relevant to manufacturing-related R&D. Additional information will be posted on the NIH Small Business Funding Opportunities Web site (http://grants.nih.gov/grants/funding/sbir.htm) and in the NIH Guide for Grants and Contracts as it becomes available. Small businesses may be interested in reading a U.S. Department of Commerce 2004 report, "Manufacturing in America: A Comprehensive Strategy to Address the Challenges to U.S. Manufacturers."

C. AWARDING COMPONENTS

The following awarding components are participating in this SBIR Solicitation for Contract Proposals.

National Institutes of Health (NIH)

- National Cancer Institute (NCI)
- National Heart, Lung, and Blood Institute (NHLBI)
- National Institute on Alcohol Abuse and Alcoholism (NIAAA)
- National Institute on Drug Abuse (NIDA)
- National Institute of Mental Health (NIMH)

Centers for Disease Control and Prevention (CDC)

- National Center on Birth Defects and Developmental Disabilities (NCBDDD)
- Coordinating Office for Terrorism Preparedness and Emergency Response (COTPER)
- Immunization Safety Office (ISO)

D. SBIR PROGRAM ELIGIBILITY

Organizational Criteria: Each organization submitting a proposal under the SBIR program must qualify as a small business concern as defined in Section III. In determining whether an offeror is a small business concern, an assessment will be made of several factors, including whether or not it is independently owned and operated and whether or not it is an affiliate of a larger organization whose employees, when added to those of the offeror organization, exceed 500. In conducting this assessment, all appropriate factors will be considered, including common ownership, common management, and contractual relationships.

In accordance with 13 C.F.R. 121.103, affiliation exists when "… one concern controls or has the power to control the other … control may be affirmative or negative, …it does not matter whether control is exercised, so long as the power to control exists." One of the circumstances that would lead to a finding that an organization is controlling or has the power to control another organization involves sharing common office space and/or employees and/or other facilities (e.g., laboratory space). 13 C.F.R. 121.103 also states that control or the power

to control exists when "… key employees of one concern organize a new concern … and serve as its officers, directors, principal stockholders, and/or key employees; and one concern is furnishing or will furnish the other concern with subcontracts, financial or technical assistance, and/or other facilities, whether for a fee or otherwise."

Joint ventures and limited partnerships are eligible provided the entity created qualifies as a small business concern as defined in Section III of this solicitation.

Access to special facilities or equipment in another organization is permitted (as in cases where the SBIR awardee has entered into a subcontractual agreement with another institution for a specific, limited portion of the research project). However, *research space occupied by an SBIR contractor organization must be space that is available to and under the control of the SBIR contractor for the conduct of its portion of the project*. Where there is indication of sharing of common employees, a determination will be made on a case-by-case basis of whether or not such sharing constitutes control or the power to control.

Whenever a proposed SBIR project is to be conducted in facilities other than those of the offeror, a letter must be submitted *with* the proposal stating that leasing/rental arrangements have been negotiated for appropriate research space (i.e., space that will be available to and under the control of the SBIR contractor organization).

This letter must be signed by an *authorized official of the organization whose facilities are to be used for the SBIR project*. It also must include a description of the facilities and, if appropriate, equipment that will be leased/rented to the offeror organization.

If it appears that an offeror does not meet eligibility requirements, the NIH/CDC will request an eligibility determination of the organization from the cognizant SBA Government Contracting Area Office. The evaluation of the proposal for scientific merit will be deferred until the SBA provides a determination.

Project Director/Principal Investigator Criteria. The primary employment of the Project Director/Principal Investigator (PD/PI) must be with the offeror at the time of contract award and during the conduct of the proposed project. The PD/PI is the single individual designated in the proposal with responsibility for the scientific and technical direction of the project. Primary employment means that *more than one half of the PD/PI's time* is spent in the employ of the small business concern. *Primary employment with a small business concern precludes full-time employment at another organization*.

In the event that the PD/PI: (1) is a less-than-full-time employee of the small business, (2) is concurrently employed by another organization, or (3) gives the appearance of being concurrently employed by another organization, whether for a paid or unpaid position, at the time of submission of the proposal, *it is essential that documentation be submitted with the proposal to verify his/her eligibility*. If the PD/PI also is employed or appears to be employed by an organization other than the offeror (e.g., a university, a nonprofit research institute, or another company), a letter must be provided by the *non-offeror organization* confirming that the PD/PI will, if awarded an SBIR contract, become a less-than-half-time employee of such organization and will remain so for the duration of the SBIR project. If the PD/PI is employed by a university, the Dean's Office must provide such a letter. If the PD/PI is employed by another for-profit organization, the corporate official must sign the letter. This documentation is required for every proposal that is submitted, even one that is a revision of a previously submitted proposal.

NEW ***Multiple Principle Investigators.*** Offerors may propose a multiple Project Director/Principal Investigator (PD/PI) model to direct the project or program to be supported by the contract. The multiple PD/PI model is intended to supplement, and not replace, the traditional single PI model. Ultimately, the decision to submit a proposal using the multiple PD/PI versus single PD/PI is the decision of the investigators and their organizations. The decision whether to employ multiple PDs/PIs should be consistent with and justified by the scientific goals of the project.

For Multiple PD/PI proposals: The first PI listed must be affiliated with the applicant small business concern organization submitting the proposal and will serve as the **Contact PD/PI**. For both SBIR Phase I and SBIR Phase II, the *primary employment of the "Contact PD/PI" must be with the small business concern at the time of award and during the conduct of the proposed project.*

Performance Site Criteria. For both Phase I and Phase II, the research or R&D project activity *must be performed in its entirety in the United States (see* Section III. Definitions*)*.

Market Research. *The NIH/CDC will not support any market research under the SBIR program*. Neither will it support studies of the literature that will lead to a new or expanded statement of work. Literature searches where the commercial product is a database are acceptable.

For purposes of the SBIR program, "market research" is the systematic gathering, recording, computing, and analyzing of data about problems relating to the sale and distribution of the subject of the research project. It includes various types of research, such as the size of potential market and potential sales volume, the identification of consumers most apt to purchase the products, and the advertising media most likely to stimulate their purchases. However, "market research" does not include activities under a research plan or protocol that require a survey of the public as part of the objective of the project to determine the impact of the subject of the research on the behavior of individuals.

II. AGENCY CONTACT FOR INFORMATION

Web Site. The NIH SBIR/STTR Web Site at http://grants.nih.gov/grants/funding/sbir.htm offers electronic access to SBIR solicitations, abstracts of ongoing SBIR projects, the latest updates on the SBIR program, hyperlinks to sources of business assistance, and other useful information.

Technical Questions about Solicitation Topics or Contract Administration. Technical questions about a particular contract topic and general questions on the administration of an SBIR contract should be directed to the appropriate contracting officer listed in Section X. Contracting Officers and Addresses for Mailing and Delivery of Proposals.

General Questions about the NIH SBIR Program

Ms. Jo Anne Goodnight
NIH SBIR/STTR Program Coordinator
6705 Rockledge Drive
Rockledge I, Room 3540
Bethesda, MD 20892-7963
Phone: 301-435-2688 Fax: 301-480-0146
Email: sbir@od.nih.gov

Ms. Kay Etzler
NIH SBIR/STTR Program Analyst
6705 Rockledge Drive
Rockledge I, Room 3535
Bethesda, MD 20892-7963
Phone: 301-435-2713 Fax: 301-480-0146
Email: sbir@od.nih.gov

General Questions about the CDC SBIR Program

Dr. Denise Burton
Office of Public Health Research (OPHR)
Office of the Chief Science Officer
Phone: 404-639-4641
Email: DBurton2@cdc.gov

Ms. Susan Clark
Office of Public Health Research (OPHR)
Office of the Chief Science Officer
Phone: 404-639-4795
Email: sclark@cdc.gov

Listserv. The NIH maintains a ListServ e-mail broadcast service. To stay in touch with SBIR opportunities and receive notices about upcoming conferences and solicitations, subscribe by sending an email to LISTSERV@LIST.NIH.GOV with the following text in the message body: subscribe listname your name, where listname is the name of the list you wish to subscribe to, and your name is your name. (LISTSERV will get your e-mail address from the "From:" address of your e-mail message.)

III. DEFINITIONS

Affiliate. This term has the same meaning as set forth in 13 C.F.R. Part 121 – Small Business Size Regulations, §121.103, *"How does the SBA determine affiliation?"*

Child. The NIH Policy on Inclusion of Children as Participants in Research Involving Human Subjects defines a child as an individual under the age of 21 years. The intent of the NIH policy is to provide the opportunity for children to participate in research studies when there is a sound scientific rationale for including them, and their participation benefits children and is appropriate under existing Federal guidelines. Thus, children must be included in NIH conducted or supported clinical research unless there are scientific and ethical reasons not to include them.

HHS Regulations (45 C.F.R. Part 46, Subpart D, Sec.401-409) provide additional protections for children involved as subjects in research, based on this definition: "Children are persons who have not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted." Generally, state laws define what constitutes a "child." Consequently, the

age at which a child's own consent is required and sufficient to participate in research will vary according to state law. For example, some states consider a person age 18 to be an adult and therefore one who can provide consent without parental permission.

Clinical Research. NIH defines human clinical research as: *(1)* Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are *in vitro* studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies. *(2)* Epidemiologic and behavioral studies. *(3)* Outcomes research and health services research.

Studies falling under Exemption 4 for human subjects research are not considered clinical research by this definition.

Clinical Trial. The NIH defines a clinical trial as a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious and effective.

Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits this definition of a clinical trial.

Human subjects research to develop or evaluate clinical laboratory tests (e.g. imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test will be used for medical decision making for the subject or the test itself imposes more than minimal risk for subjects.

Biomedical clinical trials of experimental drug, treatment, device or behavioral intervention may proceed through four phases:

- *Phase I* clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects).
- *Phase II* clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.
- *Phase III* studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.
- *Phase IV* studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.
- *NIH-Defined Phase III Clinical Trial*. For the purpose of the Guidelines, an NIH-defined Phase III clinical trial is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

Commercialization. The process of developing markets and producing and delivering products for sale (whether by the originating party or by others); as used here, commercialization includes both government and private sector markets.

Consultant. An individual who provides professional advice or services for a fee, but normally not as an employee of the engaging party. In unusual situations, an individual may be both a

consultant and an employee of the same party, receiving compensation for some services as a consultant and for other work as a salaried employee. To prevent apparent or actual conflicts of interest, grantees and consultants must establish written guidelines indicating the conditions of payment of consulting fees. Consultants may also include firms that provide paid professional advice or services.

Also see FAR 31.205-33, Professional and consultant service costs.

Contract. An award instrument establishing a binding legal procurement relationship between a funding agency and the recipient, obligating the latter to furnish an end product or service and binding the agency to provide payment therefore.

Essentially Equivalent Work. This term is meant to identify "scientific overlap," which occurs when: (1) substantially the same research is proposed for funding in more than one proposal (contract proposal or grant application) submitted to the same Federal agency; OR (2) substantially the same research is submitted to two or more different Federal agencies for review and funding consideration; OR (3) a specific research objective and the research design for accomplishing that objective are the same or closely related in two or more proposals or awards, regardless of the funding source.

Feasibility. The extent to which a study or project may be done practically and successfully.

Funding Agreement. Any grant, contract, or cooperative agreement entered into between any Federal agency and any small business concern for the performance of experimental, developmental, or research work, including products or services, funded in whole or in part by the Federal Government.

Human Subjects. The HHS regulations "Protection of Human Subjects" (45 CFR Part 46, administered by OHRP) define a human subject as a living individual about whom an investigator conducting research obtains:

- data through *intervention* or *interaction* with the individual or
- identifiable *private information*

Research that involves obtaining private information or human biological specimens (such as blood and tissue samples) that can be linked by the investigator(s) to living individuals is considered human subjects research.

Research that involves only coded private information/data or coded human biological specimens may or may not constitute human subjects research under the HHS human subjects regulations (45 CFR 46).

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject.

The use of autopsy materials is governed by applicable state and local law and is not directly regulated by 45 C.F.R. Part 46.

Innovation. Something new or improved, including research for: (1) development of new technologies, (2) refinement of existing technologies, or (3) development of new applications for existing technologies. For the purposes of PHS programs, an example of "innovation" would be new medical or biological products, for improved value, efficiency, or costs.

Intellectual Property. The separate and distinct types of intangible property that are referred to collectively as "intellectual property," including but not limited to: patents, trademarks, copyrights, trade secrets, SBIR technical data (as defined in this section), ideas, designs, know-how, business, technical and research methods, and other types of intangible business assets, and including all types of intangible assets either proposed or generated by an SBC as a result of its participation in the SBIR program.

Joint Venture. An association of concerns with interests in any degree or proportion by way of contract, express or implied, consorting to engage in and carry out a single specific business venture for joint profit, for which purpose they combine their efforts, property, money, skill, or knowledge, but not on a continuing or permanent basis for conducting business generally. A joint venture is viewed as a business entity in determining power to control its management.

For additional information, see http://www.sba.gov/library/cfrs/13cfr121.html

Key Personnel Engaged on Project. In addition to the PD/PI, Key Personnel are defined as individuals who contribute to the scientific development or execution of the project in a substantive, measurable way, whether or not salaries are requested.

Typically, these individuals have doctoral or other professional degrees, although individuals at the masters or baccalaureate level should be included if their involvement meets the definition of Key Personnel. Consultants should also be included if they meet the definition of Key Personnel. Key Personnel must devote measurable effort to the project whether or not salaries are requested--"zero percent" effort or "as needed" are not acceptable levels for those designated as Key Personnel.

Manufacturing-related R&D as a result of Executive Order 13329. Encompasses improvements in existing methods or processes, or wholly new processes, machines or systems. Four main areas include:

1. *Unit process level technologies* that create or improve manufacturing processes including:
    - fundamental improvements in existing manufacturing processes that deliver substantial productivity, quality, or environmental benefits.
    - development of new manufacturing processes, including new materials, coatings, methods, and associated practices.
2. *Machine level technologies* that create or improve manufacturing equipment, including:
    - improvements in capital equipment that create increased capability (such as accuracy or repeatability), increased capacity (through productivity improvements or cost reduction), or increased environmental efficiency (safety, energy efficiency, environmental impact).
    - new apparatus and equipment for manufacturing, including additive and subtractive manufacturing, deformation and molding, assembly and test, semiconductor fabrication, and nanotechnology.
3. *Systems level technologies* for innovation in the manufacturing enterprise, including:
    - advances in controls, sensors, networks, and other information technologies that improve the quality and productivity of manufacturing cells, lines, systems, and facilities.
    - innovation in extended enterprise functions critical to manufacturing, such as quality systems, resource management, supply change integration, and distribution, scheduling and tracking.
    - technologies that enable integrated and collaborative product and process development, including computer-aided and expert systems for design, tolerancing, process and materials selection, life-cycle cost estimation, rapid prototyping, and tooling.
4. *Environment or societal level technologies* that improve workforce abilities, productivity, and manufacturing competitiveness, including:
    - technologies for improved workforce health and safety, such as human factors and ergonomics.
    - technologies that aid and improve workforce manufacturing skill and technical excellence, such as educational systems incorporating improved manufacturing knowledge and instructional methods.

Principal Investigator, Program Director, or Project Director (PD/PI). The individual(s) judged by the offeror organization to have the appropriate level of authority and responsibility to direct the project or program to be supported by the award. The offeror organization may designate multiple individuals as principal investigators (PDs/PIs) who share the authority and responsibility for leading and directing the project, intellectually and logistically. When multiple PD/PIs are named, each is responsible and accountable to the offeror organization, or as appropriate, to a collaborating organization for the proper conduct of the project or program including the submission of all required reports. The presence of more than one PD/PI on a proposal or award diminishes neither the responsibility nor the accountability of any individual PD/PI.

Prototype. A model of something to be further developed that includes designs, protocols, questionnaires, software, devices, etc.

Research or Research and Development (R/R&D). Any activity that is:

- A systematic, intensive study directed toward greater knowledge or understanding of the subject studied.
- A systematic study directed specifically toward applying new knowledge to meet a recognized need.
- A systematic application of knowledge toward the production of useful materials, devices, and systems or methods, including design, development, and improvement of prototypes and new processes to meet specific requirements.

SBIR Technical Data. All data generated during the performance of an SBIR award.

SBIR Technical Data Rights. The rights a small business concern obtains in data generated during the performance of any SBIR Phase I, Phase II, or Phase III award that an awardee delivers to the Government during or upon completion of a Federally-funded project, and to which the Government receives a license.

Small Business Concern. A small business concern is one that, at the time of award of Phase I and Phase II, meets *all* of the following criteria:

1. Organized for profit, with a place of business located in the United States, which operates primarily within the United States or which makes a significant contribution to the United States economy through payment of taxes or use of American products, materials or labor;
2. In the legal form of an individual proprietorship, partnership, limited liability company, corporation, joint venture, association, trust or cooperative, except that where the form is a joint venture, there can be no more than 49 percent participation by business entities in the joint venture;
3. At least 51 percent owned and controlled by one or more individuals who are citizens of, or permanent resident aliens in, the United States, or it must be a for-profit business concern that is at least 51% owned and controlled by another for-profit business concern that is at least 51% owned and controlled by one or more individuals who are citizens of, or permanent resident aliens in, the United States -- (except in the case of a joint venture);
4. Has, including its affiliates, not more than 500 employees. and , and meets the other regulatory requirements found in 13 C.F.R. Part 121. Business concerns, other than investment companies licensed, or state development companies qualifying under the Small Business Investment Act of 1958, 15 U.S.C. 661, et seq., are affiliates of one another when either directly or indirectly, (a) one concern controls or has the power to control the other; or (b) a third-party/parties controls or has the power to control both.

Control can be exercised through common ownership, common management, and contractual relationships. The term "affiliates" is defined in greater detail in 13 C.F.R. 121.3-2(a). The term "number of employees" is defined in 13 C.F.R. 121.3-2(t).

Business concerns include, but are not limited to, any individual (sole proprietorship), partnership, corporation, joint venture, association, or cooperative. Further information may be obtained by contacting the Small Business Administration Size District Office at http://sba.gov/size.

Socially and Economically Disadvantaged Individual. A member of any of the following groups: Black Americans; Hispanic Americans; Native Americans; Asian-Pacific Americans; Subcontinent Asian Americans; other groups designated from time to time by the Small Business Administration (SBA) to be socially disadvantaged; or any other individual found to be socially and economically disadvantaged by SBA pursuant to Section 8(a) of the Small Business Act, 15 U.S.C. 637(a).

Socially and Economically Disadvantaged Small Business Concern. A socially and economically disadvantaged small business concern is one that is at least 51% owned and controlled by one or more socially and economically disadvantaged individuals, or an Indian tribe, including Alaska Native Corporations (ANCs), a Native Hawaiian Organization (NHO), or a Community Development Corporation (CDC). Control includes both the strategic planning (as that exercised by boards of directors) and the day-to-day management and administration of business operations. See 13 C.F.R. 124.109, 124.110, and 124.111 for special

rules pertaining to concerns owned by Indian tribes (including ANCs), NHOs or CDCs, respectively.

Subcontract. Any agreement, other than one involving an employer-employee relationship, entered into by a Federal Government prime contractor calling for supplies or services required solely for the performance of the prime contract or another subcontract.

United States. The fifty states, the territories and possessions of the Federal Government, the Commonwealth of Puerto Rico, the Republic of the Marshall Islands, the Federated States of Micronesia, the Republic of Palau, and the District of Columbia.

Women-Owned Small Business Concern. A small business concern that is at least 51 percent owned by one or more women, or in the case of any publicly owned business, at least 51 percent of the stock is owned by women, and women control the management and daily business operations.

IV. PHASE I PROPOSAL PREPARATION INSTRUCTIONS AND REQUIREMENTS

A. LIMITATIONS ON LENGTH OF PROPOSAL

SBIR Phase I proposals must not exceed 25 single-sided, single-spaced pages, including the cover sheet, abstract, cost breakdown, and all enclosures or attachments. Pages should be of standard size (8 l/2" X 11"), and you should use an Arial, Helvetica, Palatino Linotype or Georgia typeface and a font size of 11 points or larger. Excluded from the 25-pages are cover letters, Human Subjects Research and Vertebrate Animal information, letters of commitment from collaborators and consultants and letters to determine eligibility, and, if applicable, the list of prior SBIR Phase II awards (see Section IV.F). Unless specifically solicited by a Contracting Officer, no other appendices or attachments may be submitted, and if submitted, they will not be considered in the evaluation of scientific and technical merit. Proposals in excess of the page limitation shall not be considered for review or award.

B. PROPOSAL COVER SHEET

Complete the form identified as Appendix A (MS Word | PDF), and use it as the first page of the proposal. *No other cover sheet should be used*.

If submitting a proposal reflecting Multiple Project Directors/Principal Investigators (PDs/PIs), the individual designated as the Contact PI should be entered here.

- ***Topic Number.*** Provide the appropriate numerical designator of the research topic for which your proposal is being submitted. If your proposal is responsive to a subtopic, provide both the topic and subtopic numbers. (A numerical or alphabetical designator precedes each topic and subtopic.)

- ***Project Title.*** Select a title that reflects the substance of the project. Do not use the title of the topic that appears in the solicitation.

C. ABSTRACT OF RESEARCH PLAN

Complete the form identified as Appendix B (MS Word | PDF), and insert it as the second page of each proposal. Abstracts of successful proposals will be published by NIH and, therefore, should not contain proprietary information. The abstract should include a brief description of the problem or opportunity, specific aims, and a description of the effort. Summarize anticipated results and potential commercial applications of the proposed research.

D. RESEARCH PLAN

Any research proposal involving the collection of information, such as surveys or interviews, of 10 or more public respondents will require clearance by the U.S. Office of Management and Budget. Therefore, it is not practical to propose such an activity for Phase I, which normally has only a six-month duration.

Beginning on page three of the proposal, discuss in the order indicated the following elements:

1. ***Identification and Significance of the Problem or Opportunity.*** Provide a clear statement of the specific technical problem or opportunity addressed.
2. ***Technical Objectives.*** State the specific objectives of the Phase I effort, including the technical questions it will try to answer to determine the feasibility of the proposed approach.
3. ***Work Plan.*** Provide a detailed plan for the R&D to be carried out, including the experimental design, procedures, and protocols to be used. Address the objectives and the

questions stated in Item 2 above. Discuss in detail the methods to be used to achieve each objective or task. For specific guidance and instructions related to Human Subjects research, please see the section entitled, "Human Subjects Research and Protection from Risk" and the "Human Subjects Research Guidance and Information Supplement."

4. ***Related Research or R&D.*** Describe significant research or R&D that is directly related to the proposal, including any conducted by the Project Director/Principal Investigator (PD/PI) or by the proposing firm. Describe how it relates to the proposed effort and any planned coordination with outside sources. *The PD/PI must persuade reviewers of his or her awareness of recent significant research or R&D conducted by others in the same scientific field*.

5. ***Relationship with Future R&D.***

   a. State the results expected from the proposed approach.

   b. Discuss the significance of the Phase I effort in providing a foundation for the Phase II R/R&D effort.

6. ***Potential Commercial Applications.*** Describe why the proposed project appears to have potential commercial applications, and whether and by what means the proposed project appears to have potential use by the Federal Government.

7. ***Key Personnel and Bibliography of Directly Related Work.*** Identify key personnel, including their directly related education, experience, and bibliographic information. Where resumes are extensive, focus on summaries of the most relevant experience or publications. *Provide dates and places of employment* and some information about the nature of each position or professional experience. Resumes must identify the current or most recent position.

   Multiple PD/PI Leadership Plan. For proposals designating multiple PDs/PIs, a leadership plan must be included. A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team and the research project should be described, including communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the project or program should be delineated for the PDs/PIs and other collaborators.

   If budget allocation is planned, the distribution of resources to specific components of the project or the individual PDs/PIs should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in Contract Award.

8. ***Consultants.*** Involvement of consultants in the planning and/or research stages of the project is permitted. However, such use must be described in detail and supported by appropriate letters from each individual confirming his/her role in the project.

9. ***Facilities and Equipment.*** Indicate where the proposed research will be conducted. *One of the performance sites must be the offeror organization*. Describe the facilities to be used; identify the location; and briefly indicate their capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Include clinical, computer, and office facilities of the offeror and those of any other performance sites to be used in the project.

   List the most important equipment items already available for this project, noting location and pertinent capabilities of each.

   Any equipment and products purchased with Government funds shall be American-made, to the extent possible.

   Title to Equipment. Title to equipment purchased with Government funding by the SBIR awardee in relation to project performance vests upon acquisition in the Federal Government. However, the Government may transfer such title to an SBIR awardee upon expiration of the project where the transfer would be more cost-effective than recovery of the property.

E. CURRENT AWARDS AND PENDING PROPOSALS/APPLICATIONS

A small business concern may not submit both a contract proposal and a grant application for essentially the same project to the same or different awarding component(s) of the NIH/CDC. The only exception would be the submission of a grant application after a contract proposal has been evaluated and is no longer being considered for

award. A firm that receives a Phase I SBIR contract may be solicited to submit a Phase II grant application and vice versa.

While it is permissible, with proposal notification, to submit identical proposals or proposals containing a significant amount of essentially equivalent work (as defined in this solicitation) for consideration under numerous Federal program solicitations, it is unlawful to enter into contracts or grants requiring essentially equivalent effort.

If there is any question concerning this, it must be disclosed to the soliciting agency or agencies before award.

If a firm elects to submit identical proposals or proposals containing a significant amount of essentially equivalent work under other Federal program solicitations, include a statement in each such proposal indicating the information requested in items 1-10 set forth below.

In addition, provide the information requested in items 1-10 on (a) active funding through contracts, grants, and cooperative agreements from public or private sponsors; (b) contract proposals and grant and cooperative agreement applications pending review or funding; and (c) contract proposals and grant and cooperative agreement applications about to be submitted.

1. Name and address of the funding source.
2. Type of award (contract, grant, cooperative agreement) and identifying number.
3. Title of research project.
4. Name and title of Principal Investigator(s) or Project Manager(s).
5. Hours per week on the project by the Principal Investigator(s) or Project Manager(s).
6. Annual costs proposed or awarded.
7. Entire period of support.
8. Date of proposal/application submission or date of award.
9. Title, number, and date of solicitations under which proposals or applications were submitted or awards received.
10. The specific applicable research topic for each SBIR proposal or application submitted or award received. *Specifically identify those projects that are SBIR*.

F. PRIOR SBIR PHASE II AWARDS

If the small business concern has received more than 15 Phase II awards in the prior 5 fiscal years, submit name of awarding agency, date of award, funding agreement number, amount, topic or subtopic title, follow-on agreement amount, source, and date of commitment and current commercialization status for each Phase II.

This information must be submitted with the proposal, but is excluded from the 25-page limitation.

G. PROPOSED COST BREAKDOWN

Complete the form identified as Appendix C (Contract Pricing Proposal) (MS Word | PDF). The cost breakdown should appear as the last section of the proposal. *If some items on this form do not apply to the proposed project, they need not be completed*.

- Under “Government Solicitation No.,” enter “PHS 2008-1.”
- If supplies are proposed, provide the quantities and the price per unit.
- Under “Direct Labor,” *list all key personnel by name*. Support personnel may be consolidated into categories or labor classes, e.g., research assistants or data processing clerks.
- If travel is proposed, provide the following details on “Exhibit A – Supporting Schedule”: destination(s); duration of trip(s); number of travelers; and cost per trip, broken down by cost elements, e.g., airfare, lodging, and meals.
- If consultants are proposed, provide name(s), rate(s), and number of hours/days.
- If a subcontract is proposed, provide the same type of detailed cost breakdown as required for Appendix C. *Also provide a copy of the subcontractual agreement*.
- Use “Exhibit A – Supporting Schedule” to itemize and justify all major cost elements. If more space is needed, use Page 3 of Appendix C.

- *Normally, at least two-thirds or 67% of the entire research or analytical effort must be carried out by the offeror*, i.e., subcontracts for portions of the scientific/technical effort and consultant fees normally may not exceed 33% of the total cost breakdown.

H. STREAMLINING THE CONTRACTING PROCESS

With the Federal Acquisition Streamlining Act of 1994 and the Federal Acquisition Reform Act of 1996, a number of terms and conditions that previously applied to contracts under $100,000 are no longer applicable. Under the SBIR program, Phase I awards, which normally may not exceed $100,000, will reflect the streamlined contract document.

The NIH uses special *"just in time" procedures* that are designed to reduce the administrative burden on offerors without compromising the information needed during the initial evaluation of proposals. Certain documents that would previously have been required for submission with the Phase II proposal will be requested at a later stage in the evaluation process. The following documentation is part of the "just in time" procedures and offerors who elect to submit proposals under the *"Fast-Track" initiative* below are not required to submit this documentation with their initial Phase II business proposal:

- ***Travel Policy.*** The offeror's written travel policy.
- ***Annual Financial Report.*** The offeror's most recent annual financial report.
- ***Total Compensation Plan.*** Salary and fringe benefits of professional employees under service contracts.
- ***Data Substantiating the Costs and Prices Proposed.*** That is, payroll documentation, vendor quotes, invoice prices, etc.

I. REQUIREMENT FOR ADEQUATE ASSURANCE OF PROTECTION OF HUMAN SUBJECTS

The HHS regulations for the Protection of Human Subjects, 45 C.F.R. 46 (as amended), provide a systematic means, based on established ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the HHS. *The requirement is that an approved assurance of compliance with the regulations must be on file with the Office for Human Research Protections (OHRP), DHHS (*http://www.hhs.gov/ohrp*) before an HHS award can be made.*

Neither an Institutional Review Board (IRB) review nor an OHRP-approved Assurance is required at the time the proposal is submitted or at the time that the proposals are peer reviewed.

Human Subjects Research and Protection from Risk

This information must be submitted with the proposal, but is excluded from the 25-page limitation.

In the Human Subjects Research section of the Research Plan, you must provide sufficient information for reviewers to determine that the proposed research meets (1) the requirements of the HHS regulations to protect human subjects from research risks (45 CFR Part 46), (2) the requirements of NIH policies for data and safety monitoring of clinical trials, and (3) the requirements of NIH policies on inclusion of women, minorities, and children.

Provided in the Human Subjects Research Guidance and Information Supplement is a table that presents six possible research scenarios, and links to the instructions for providing information on human subjects protection information and the inclusion of women, minorities, and children specific to each scenario. All research will fall into one of these six scenarios. Which scenario best matches your proposed research depends on your answers to the following five questions:

Question 1: Does your proposed research involve human subjects?

Question 2: Does your proposed human subjects research meet the criteria for one or more of the exemptions in the HHS regulations (45 C.F.R. 46)?

Question 3: Does your proposed research meet the definition of clinical research?

Question 4: Does your proposed research include a clinical trial?

Question 5: Does your proposed research meet criteria for an NIH-Defined Phase III Clinical Trial?

If you answer "Yes" to any of the five questions, proceed to the table below, select the scenario that best matches your responses and then follow the instructions located on the scenario pages.

If you need additional guidance then click on the questions or the column heading in the table below and you will be provided additional information and guidance.

Much of the information on the protection of human subjects that you are required to provide in this section is identical to information that will be required for IRB review.

J. REQUIREMENT FOR ADEQUATE ASSURANCE OF COMPLIANCE WITH THE PHS POLICY ON HUMANE CARE AND USE OF LABORATORY ANIMALS

Instructions and Required Information

This information must be submitted with the proposal, but is excluded from the 25-page limitation.

Create a section heading entitled **"Vertebrate Animals."** Place it immediately following the "Research Plan" section of the proposal (or after Human Subjects Research section, if applicable).

Under the Vertebrate Animals heading, address the following five points. In addition, when research involving vertebrate animals will take place at collaborating site(s) or other performance site(s), provide this information before discussing the five points. Although no specific page limitation applies to this section of the proposal, be succinct.

1. Provide a detailed description of the proposed use of the animals in the work outlined in the Research Design and Methods section. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work.
2. Justify the use of animals, the choice of species, and the numbers to be used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and numbers.
3. Provide information on the veterinary care of the animals involved.
4. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices, where appropriate, to minimize discomfort, distress, pain, and injury.
5. Describe any method of euthanasia to be used and the reasons for its selection. State whether this method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. If not, present a justification for not following the recommendations.

Guidance and Additional Instructions

NIH no longer requires Institutional Animal Care and Use Committee approval of the proposed research before NIH peer review of a proposal (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-064.html).

In August, 2002 NIH announced an IACUC "just-in-time" process for applications submitted for the October 1, 2002 deadline or other deadlines where the applications had a May/June 2003 Council review. The PHS policy requirement that no award may be made without an approved Assurance and without verification of IACUC approval remains in effect. The new policy gave institutions flexibility in the timing of IACUC review relative to the submission of a proposal and the verification of IACUC review. The policy does not require that IACUC approval be deferred. Institutional officials retain the discretion to require IACUC approval prior to NIH peer review in circumstances of their choosing if deemed necessary. As part of the NIH peer review process, the scientific review group will continue to address the adequacy of animal usage and protections in the review of a proposal and will continue to raise any concerns about animal welfare issues. Verification of IACUC approval will be required in a "just-in-time" fashion prior to award.

The PHS *Policy on Humane Care and Use of Laboratory Animals* requires that offeror organizations proposing to use vertebrate animals file a written Animal Welfare Assurance with the Office of Laboratory Animal Welfare (OLAW), establishing appropriate policies and procedures to ensure the humane care and use of live vertebrate animals involved in research activities supported by the PHS. The PHS policy stipulates that an offeror organization, whether domestic or foreign, bears responsibility for the humane care and use of animals in PHS-supported research activities. This policy implements and supplements the *U.S. Government Principles for the Utilization and Care of*

Vertebrate Animals Used in Testing, Research, and Training and requires that institutions use the *Guide for the Care and Use of Laboratory Animals* as a basis for developing and implementing an institutional animal care and use program. This policy does not affect applicable state or local laws or regulations that impose more stringent standards for the care and use of laboratory animals. All institutions are required to comply, as applicable, with the Animal Welfare Act as amended (7 USC 2131 et sec.) and other Federal statutes and regulations relating to animals. These documents are available from the Office of Laboratory Animal Welfare, National Institutes of Health, Bethesda, MD 20892, (301) 496-7163.

The PHS Policy defines “animal” as “any live, vertebrate animal used or intended for use in research, research training, experimentation or biological testing or for related purposes.”

No PHS award for research involving vertebrate animals will be made to an offeror organization unless that organization is operating in accordance with an approved Animal Welfare Assurance and provides verification that the IACUC has reviewed and approved the proposed activity in accordance with the PHS policy. Proposals may be referred by the PHS back to the IACUC for further review in the case of apparent or potential violations of the PHS policy. No award to an individual will be made unless that individual is affiliated with an assured organization that accepts responsibility for compliance with the PHS policy. Foreign offeror organizations applying for PHS awards for activities involving vertebrate animals are required to comply with PHS policy or provide evidence that acceptable standards for the humane care and use of animals will be met.

K. LIMITATIONS ON USE OF APPROPRIATED FUNDS

The Department of the Health Human Services Appropriation Act, 2007 (Public Law 110-005), Revised Continuing Appropriations Resolution, 2007, limits the use of appropriated funds on NIH grant, cooperative agreement, and contract awards for Fiscal Year 2007, as specified below. It is anticipated that these limitations will continue in subsequent fiscal years.

Salary Rate Limitation

Public Law 110-005 restricts the use of Federal funds to pay the direct salary of an individual under an NIH grant, cooperative agreement, or applicable contract, at a rate in excess of Executive Schedule, Level I. The salary rate limitation also applies to individuals proposed under subcontracts; however, it does not apply to consultants. The legislation also does not apply to firm fixed price contracts. Effective January 1, 2007, the Executive Level I salary is $186,000 per year.

Anti-Lobbying (for contracts exceeding $100,000)

"(a) No part of any appropriation contained in this Act shall be used, other than for normal and recognized executive-legislative relationships, for publicity or propaganda purposes, for the preparation, distribution, or use of any kit, pamphlet, booklet, publication, radio, television, or video presentation designed to support or defeat legislation pending before the Congress or any State legislature, except in presentation to the Congress or any State legislature itself. (b) No part of any appropriation contained in this Act shall be used to pay the salary or expenses of any grant or contract recipient, or agent acting for such recipient, related to any activity designed to influence legislation or appropriations pending before the Congress or any State legislature."

Restriction on Distribution of Sterile Needles

"Notwithstanding any other provision of this Act, no funds appropriated under this Act shall be used to carry out any program of distributing sterile needles or syringes for the hypodermic injection of any illegal drug."

Acknowledgment of Federal Funding

"When issuing statements, press releases, requests for proposals, bid solicitations and other documents describing projects or programs funded in whole or in part with Federal money, all grantees receiving Federal funds included in this Act, including but not limited to State and local governments and recipients of Federal research grants, shall clearly state: (1) the percentage of the total costs of the program or project which will be financed with Federal money; (2) the dollar amount of Federal funds for the project or program; and (3) percentage and dollar amount of the total costs of the project or program that will be financed by non-governmental sources."

Restriction on Abortions

"(a) None of the funds appropriated under this Act, and none of the funds in any trust fund to which funds are appropriated in this Act, shall be expended for any abortion."

Ban on Funding of Human Embryo Research

"(a) None of the funds made available in this Act may be used for: (1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.204(b) (2) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)). (b) For purposes of this section, the term "human embryo or embryos" includes any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells."

Limitation on Use of Funds for Promotion of Legalization of Controlled Substances

"(a) None of the funds made available in this Act may be used for any activity that promotes the legalization of any drug or other substance included in schedule I of the schedules of controlled substances established by section 202 of the Controlled Substances Act (21 U.S.C.812). (b) The limitation in subsection (a) shall not apply when there is significant medical evidence of a therapeutic advantage to the use of such drug or other substance or that federally sponsored clinical trials are being conducted to determine therapeutic advantage."

V. "FAST-TRACK" INITIATIVE

(Applicable Only to Proposals Submitted to NIH)

The "Fast-Track" initiative is a parallel review option available to those small business concerns (offeror organizations) whose proposals satisfy additional criteria that enhance the probability of the project's commercial success. This initiative is applicable only to NIH and only if an awarding component indicates it is accepting Fast-Track proposals for a particular topic. (Refer to Section XII, "Research Topics," for notation.)

The Fast-Track initiative is an opportunity for small business concerns to submit both a Phase I and Phase II proposal for concurrent peer review. This initiative also has the potential to minimize any funding gap between Phase I and Phase II.

Fast-Track Proposal Process

To identify the proposals as Fast-Track, check the box marked "Yes" next to the words "Fast-Track Proposal" shown on the Phase I Proposal Cover Sheet, Appendix A (MS Word | PDF).

The small business concern must submit both a Phase I and a Phase II proposal for concurrent initial peer review and evaluation. The Fast-Track proposal must consist of the following parts:

1. ***Phase I Proposal.*** Prepared in accordance with Section IV. Phase I Proposal Preparation Instructions and Requirements, and addressing all factors stated in the evaluation criteria (Section VII) for Phase I proposals.
2. ***Phase II Proposal.*** Prepared in accordance with Section VI, Fast-Track Phase II Proposal Preparation Instructions and Requirements and addressing all factors stated in the evaluation criteria (Section VII) for Phase II proposals.
3. **Commercialization Plan**

The Phase II portion of Fast-Track proposals must include a succinct Commercialization Plan. The Commercialization Plan is limited to *15 pages*. Be succinct. There is no requirement for offerors to use the maximum allowable pages allotted to the Commercialization Plan.

Create a section entitled, "Commercialization Plan," and provide a description in each of the following areas:

a. ***Value of the SBIR Project, Expected Outcomes, and Impact.*** Describe, in layperson's terms, the proposed project and its key technology objectives. Clarify the need addressed, specifying weaknesses in the current approaches to meet this need. In addition, describe the commercial applications of the research and the innovation inherent in this proposal. Be sure to also specify the potential societal, educational, and scientific benefits of this work. Explain the non-commercial impacts to the overall significance of the project. Explain how the SBIR project integrates with the overall business plan of the company.

b. ***Company.*** Give a brief description of your company including corporate objectives, core competencies, present size (annual sales level and number and types of employees), history of previous Federal and non-Federal funding, regulatory experience, and subsequent commercialization, and any current products/services that have significant sales. Include a short description of the origins of the company. Indicate your vision for the future, how you will grow/maintain a sustainable business entity, and how you will meet critical management functions as your company evolves from a small technology R&D business to a successful commercial entity.

c. ***Market, Customer, and Competition.*** Describe the market and/or market segments you are targeting and provide a brief profile of the potential customer. Tell what significant advantages your innovation will bring to the market, e.g., better performance, lower cost, faster, more efficient or effective, new capability. Explain the hurdles you will have to overcome in order to gain market/customer acceptance of your innovation.

Describe any strategic alliances, partnerships, or licensing agreements you have in place to get FDA approval (if required) and to market and sell your product.

Briefly describe your marketing and sales strategy. Give an overview of the current competitive landscape and any potential competitors over the next several years. (*It is very important that you understand and know the competition*.)

d. ***Intellectual Property (IP) Protection.*** Describe how you are going to protect the IP that results from your innovation. Also note other actions you may consider taking that will constitute at least a temporal barrier to others aiming to provide a solution similar to yours.

e. ***Finance Plan.*** Describe the necessary financing you will require, and when it will be required, as well as your plans to raise the requisite financing to launch your innovation into Phase III and begin the revenue stream. Plans for this financing stage may be demonstrated in one or more of the following ways:

- Letter of commitment of funding.
- Letter of intent or evidence of negotiations to provide funding, should the Phase II project be successful and the market need still exist.
- Letter of support for the project and/or some in-kind commitment, e.g., to test or evaluate the innovation.
- Specific steps you are going to take to secure Phase III funding.

f. ***Production and Marketing Plan.*** Describe how the production of your product/service will occur (e.g., in-house manufacturing, contract manufacturing). Describe the steps you will take to market and sell your product/service. For example, explain plans for licensing, internet sales, etc.

g. ***Revenue Stream.*** Explain how you plan to generate a revenue stream for your company should this project be a success. Examples of revenue stream generation include, but are not limited to, manufacture and direct sales, sales through value added resellers or other distributors, joint venture, licensing, service. Describe how your staffing will change to meet your revenue expectations.

Offerors are *encouraged to seek commitment(s) of funds and/or resources from an investor or partner organization for commercialization* of the product(s) or service(s) resulting from the SBIR contract.

Your Phase III funding may be from any of a number of different sources including, but not limited to: SBIR firm itself; private investors or “angels”; venture capital firms; investment companies; joint ventures; R&D limited partnerships; strategic alliances; research contracts; sales of prototypes (built as part of this project); public offering; state finance programs; non SBIR-funded R&D or production commitments from a Federal agency with the intention that the results will be used by the United States government; or other industrial firms.

Fast-Track proposals that do not contain all parts described above will be redirected for Phase I consideration only.

The Phase I and Phase II proposals will be scored individually.

Fast-Track Phase II proposals may be funded following submission of the Phase I final report, and a determination that the Phase I objectives were

met, feasibility was demonstrated, and funds are available.

VI. FAST-TRACK PHASE II PROPOSAL PREPARATION INSTRUCTIONS AND REQUIREMENTS

A. LIMITATIONS ON LENGTH OF PROPOSAL

SBIR Phase II proposals generally should not exceed a total of 150 single-spaced pages, including all enclosures and attachments. Pages should be of standard size (8 1/2" x 11") and you should use an Arial, Helvetica, Palatino Linotype or Georgia typeface and a font size of 11 points or larger. Excluded from the page limitation are cover letters and letters from collaborators and consultants.

B. TECHNICAL PROPOSAL FORMAT AND CONTENT REQUIREMENTS

1. **Phase II Technical Proposal Cover Sheet** - Use Appendix D (MS Word | PDF).
2. **Table of Contents**
3. **Abstract of the Research Plan** - Use Appendix B (MS Word | PDF). State the broad, long-term objectives and specific aims. Do not include any proprietary information. Briefly and concisely describe the research design and methods for achieving these goals.
4. **Anticipated Results of Phase I Effort** - Briefly discuss and summarize the objectives of your Phase I effort, the research activities to be carried out, and the anticipated results.
5. **Research Plan**

   a. *Detailed Approach and Methodology* - provide an explicit detailed description of the Phase II approach. This section should be the major portion of the proposal and must clearly show advancement in the project appropriate for Phase II. Indicate not only what is planned, but also how and where the work will be carried out. List all tasks in a logical sequence to precisely describe what is expected of the contractor in performance of the work. Tasks should contain detail to (1) establish parameters for the project; (2) keep the effort focused on meeting the objectives; (3) describe end products and deliverables; and (4) describe periodic/final reports required to monitor work progress under the contract. Offerors using Human Subjects or Vertebrate Animals in their research should refer to the specific instructions provided in this solicitation.

   b. *Personnel* - List by name, title, department and organization, the extent of commitment to this Phase II effort, and detail each person's qualifications and role in the project. *Provide resumes for all key staff members,* describing directly related education, experience, and relevant publications. Describe in detail any involvement of subcontractors or consultants, and *provide resumes for all key subcontractor staff. Also, include letters of commitment with proposed consultants confirming the extent of involvement and hourly/daily rate.*

   c. *Resources* - List/describe all equipment, facilities and other resources available for this project, including the offeror's clinical, computer and office facilities/equipment at any other performance site that will be involved in this project. Briefly state their capacities, relative proximity and extent of availability to this effort. *(Any equipment specifically proposed as a cost to the contract must be justified in this section as well as detailed in the budget. Equipment and products purchased with Government funds shall be American-made, to the extent possible. Title to the equipment will vest in the Government.)*

   d. *Other considerations* - Provide a brief narrative of any unique arrangements, safety procedures in place, animal welfare issues, human subjects, etc. Note: If the research plan includes the use of human subjects or animals, refer to paragraphs IV. I-K of this solicitation for further guidance.

   Multiple PD/PI Leadership Plan. For proposals designating multiple PDs/PIs, a leadership plan must be included. A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team and the research project should be described, including communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the project or program

should be delineated for the PDs/PIs and other collaborators.

If budget allocation is planned, the distribution of resources to specific components of the project or the individual PDs/PIs should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in Contract Award.

e. *Appendices*

(1) **Work Statement** – The Contracting Officer may require the offeror to develop a Statement of Work similar in format to the sample in Appendix E (MS Word | PDF). Create this from your detailed approach and methodology. It will be incorporated into the final contract document. Do not include proprietary information.

(2) **Commercialization Plan** – Required for the Phase II portion of ALL Fast-Track proposals. Comply with requirements referred to in *Section V.3.*

6. **Summary of Related Activities** - Use Appendix F (MS Word | PDF).

7. **Technical Proposal Cost Information** - Use Appendix C (MS Word | PDF). Delete the fringe benefit costs, indirect costs and fee. Prepare a separate Appendix C for each year of the contract and a summary of the entire project.

8. **Number of Copies** - Submit an original and 9 copies.

C. BUSINESS PROPOSAL FORMAT AND CONTENT REQUIREMENTS

1. **Cover Page** - Use NIH Form 2043, Proposal Summary and Data Record, Appendix G (MS Word | PDF).

2. **Proposed Cost Breakdown** - Use Appendix C (MS Word | PDF). Explain the basis for all costs and submit documentation to support all proposed costs. Prepare a separate Appendix C for each year of the contract and a summary of the entire project.

3. **Number of Copies** - Submit an original and 4 copies.

VII. METHOD OF SELECTION AND EVALUATION CRITERIA

All Phase I and Fast-Track proposals will be evaluated and judged on a competitive basis. Using the technical evaluation criteria in Section VII.B., a panel of scientists, consisting primarily of nongovernment experts knowledgeable in the disciplines or fields under review, will evaluate proposals to determine the most promising technical and scientific approaches. Each proposal will be judged on its own merit. The Agency is under no obligation to fund any proposal or any specific number of proposals in a given topic. It also may elect to fund several or none of the proposed approaches to the same topic or subtopic.

A. EVALUATION PROCESS

Your proposal will be peer reviewed by a panel of scientists selected for their competence in relevant scientific and technical fields. Each peer review panel will be responsible for evaluating proposals for scientific and technical merit. The peer review panel provides a rating, makes specific recommendations related to the scope, direction and/or conduct of the proposed research, and for those proposals recommended for award, may provide a commentary about the funding level, labor mix, duration of the proposed contract project, vertebrate animal and human subject research issues. The Institute program staff of the awarding component will conduct a second level of review. Recommendations of the peer review panel and program staff are based on judgments about not only the technical merit of the proposed research but also its relevance and potential contributions to the mission and programs of the awarding component. A Phase I or Fast-Track contract may be awarded only if the corresponding proposal has been recommended as technically acceptable by the peer review panel. *Funding for any/all acceptable proposals is not guaranteed.*

B. TECHNICAL EVALUATION CRITERIA

In considering the technical merit of each proposal, the following factors will be assessed:

FACTORS FOR PHASE I PROPOSALS	WEIGHT
1. The soundness and technical merit of the proposed approach and identification of clear measurable goals (milestones) to be achieved during Phase I. For proposals designating multiple PDs/PIs, is the leadership approach, including the designated roles and responsibilities, governance, and organizational structure, consistent with and justified by the aims of the project and the expertise of each of the PDs/PIs? (*Preliminary data are not required for Phase I proposals*.)	40%
2. The qualifications of the proposed PDs/PIs, supporting staff, and consultants.	20%
3. The potential of the proposed research for technological innovation.	15%
4. The potential of the proposed research for commercial application.	15%
5. The adequacy and suitability of the facilities and research environment.	10%

FACTORS FOR PHASE II PROPOSALS	WEIGHT
1. The scientific/technical merit of the proposed research, including adequacy of the approach and methodology, and identification of clear, measurable goals to be achieved during Phase II. For proposals designating multiple PDs/PIs, is the leadership approach, including the designated roles and responsibilities, governance, and organizational structure, consistent with and justified by the aims of the project and the expertise of each of the PDs/PIs?	30%
2. The potential of the proposed research for commercialization, as documented in the offeror's Commercialization Plan and evidenced by (a) the offeror's record of successfully commercializing its prior SBIR/STTR or other research projects, (b) commitments of additional investment during Phase II and Phase III from private sector or other non-SBIR funding sources, and (c) any other indicators of commercial potential for the proposed research.	30%
3. The qualifications of the proposed PDs/PIs, supporting staff and consultants.	25%
4. The adequacy and suitability of the facilities and research environment.	15%

C. PROPOSAL DEBRIEFING

Offerors will be notified promptly in writing if their proposals are no longer being considered for award. Offerors may request a debriefing by submitting a written request to the Contracting Officer within three days of receipt of the notification. Untimely requests may be accommodated at the Government's discretion.

D. AWARD DECISIONS

For proposals recommended for award, the awarding component considers the following:

1. Ratings resulting from the scientific/technical evaluation process;
2. Areas of high program relevance;
3. Program balance (i.e., balance among areas of research); and
4. Availability of funds.

The agency is not under any obligation to fund any proposal or make any specific number of contract awards in a given research topic area. The agency may also elect to fund several or none of the proposals received within a given topic area. The SBIR contract projects do not require establishing a competitive range or requesting final proposal revisions before reaching source selection decisions.

VIII. CONSIDERATIONS

A. AWARDS

1. The award instrument will be a contract.
2. A profit or fixed fee may be included in the proposal, as specified in Federal Acquisition Regulation (FAR) Part 15.404-4. The fee will be negotiated as an element of the potential total contract amount over and above allowable costs.
3. Phase I awards will be firm fixed price contracts. Normally, Phase II awards will be cost-plus-fixed-fee contracts.
4. Normally, Phase I contracts may not exceed $100,000. Phase II contracts normally may not exceed $750,000—including direct costs, indirect costs, and negotiated fixed fee.
5. Cost-sharing is permitted for proposals under this solicitation; however, cost sharing is not required nor will it be an evaluation factor in the consideration of your proposal. Cost-sharing is an explicit arrangement under which the contractor bears some of the burden of reasonable, allocable, and allowable contract cost. If cost-sharing is proposed, it should be reflected in your budget summary.

Approximate number of Phase I contract awards:

AWARDING COMPONENTS		NO. OF AWARDS	ESTIMATED TIME OF AWARD
National Institutes of Health (NIH)	National Cancer Institute (NCI)	59-73	Scientific and Technical Merit Review: May 2008 Anticipated Award Date: July 2008
	National Heart, Lung, and Blood Institute (NHLBI)	11-13	Scientific and Technical Merit Review: February 2008 Anticipated Award Date: July-Sept 2008
	National Institute on Alcohol Abuse and Alcoholism (NIAAA)	10	Scientific and Technical Merit Review: March 2008 Anticipated Award Date: June 2008
	National Institute on Drug Abuse (NIDA)	10-12	Scientific and Technical Merit Review: March 2008 Anticipated Award Date: August 2008
	National Institute of Mental Health (NIMH)	5	Scientific and Technical Merit Review: January 2008 Anticipated Award Date: May 2008
Centers for Disease Control and Prevention (CDC)	National Center on Birth Defects and Developmental Disabilities (NCBDDD)	1	Scientific and Technical Merit Review: February 2008 Anticipated Award Date: May 2008
	Coordinating Office for Terrorism Preparedness and Emergency Response (COTPER)	1-2	Scientific and Technical Merit Review: February 2008 Anticipated Award Date: May 2008
	Immunization Safety Office (ISO)	3-6	Scientific and Technical Merit Review: February 2008 Anticipated Award Date: May 2008

B. MONTHLY PROGRESS REPORT

Contractors will be required to submit a monthly progress report during Phase I along with their invoice. Phase II reports will be required at intervals stipulated in the terms and conditions of award.

C. FINAL REPORT

A final report is required of all Phase I and Phase II contractors. It should include a detailed description of the project objectives, the activities that were carried out, and the results obtained. **An original and two copies** of this report must be submitted as directed by the Contracting Officer not later than the expiration date of the Phase I contract.

Each Phase II "Fast-Track" contractor must submit semi-annual progress reports. A final report is required no later than the expiration date of the Phase II contract. *All reports must be submitted as specified in the contract or as directed by the Contracting Officer.*

D. PAYMENT

The Government shall make payments, including invoice and contract financing payments, by electronic funds transfer (EFT). As a condition to any payment, the contractor is required to register in the Central Contractor Registration (CCR) database before the award of a contract. The registration site for the CCR is http://www.ccr.gov.

Payments on Phase I contracts may be made on a monthly advance basis. Invoices/financing requests submitted for costs incurred under Phase II cost reimbursement contracts will be on a monthly basis unless otherwise authorized by the contracting officer.

E. LIMITED RIGHTS INFORMATION AND DATA

Proprietary Information. Information contained in unsuccessful proposals will remain the property of the offeror. The Government, however, may retain copies of all proposals. Public release of information in any proposal will be subject to existing statutory and regulatory requirements.

The Department of Health and Human Services (HHS) recognizes that, in responding to this solicitation, offerors may submit information that they do not want used or disclosed for any purpose other than for evaluation. Such data might include trade secrets, technical data, and business data (such as commercial information, financial information, and cost and pricing data). The use or disclosure of such information may be restricted if offerors identify it and the Freedom of Information Act (FOIA) does not require its release. For information to be protected, offerors must identify in the Notice of Proprietary Information (on the Proposal Cover Sheet) the page(s) on which such information appears. Any other Notice may be unacceptable to the Government and may constitute grounds for removing the proposal from further consideration without assuming any liability for inadvertent disclosure.

Unless disclosure is required by the FOIA, as determined by FOI officials of the HHS, data contained in those portions of a proposal that have been identified as containing restricted information, in accordance with the Notice of Proprietary Information, shall not be used or disclosed except for evaluation purposes.

The HHS may not be able to withhold data that has been requested pursuant to the FOIA, and the HHS FOI officials must make that determination. The Government is not liable for disclosure if the HHS has determined that disclosure is required by the FOIA.

If a contract is awarded to the offeror as a result of, or in connection with, the submission of a proposal, the Government shall have the right to use or disclose the data to the extent provided by law. Proposals not resulting in a contract remain subject to the FOIA.

Rights to Data Developed Under SBIR Funding Agreement. Rights to data, including software developed under the terms of any funding agreement resulting from a contract proposal submitted in response to this solicitation, shall remain with the awardee. However, the Government shall have the limited right to use such data for Government purposes only.

(1) Each agency must refrain from disclosing SBIR technical data to outside the Government (except reviewers) and especially to competitors of the Small Business Concern (SBC), or from using the information to produce future technical procurement specifications that could harm the SBC that discovered and developed the innovation.

(2) SBIR agencies must protect from disclosure and non-governmental use all SBIR technical data developed from work performed under an SBIR funding agreement for a period of not less than four years from delivery of the last deliverable under that agreement (either Phase I, Phase II, or Federally-funded SBIR Phase III) unless, subject to paragraph (3)of this section, the agency obtains permission to disclose such SBIR technical data from the awardee or SBIR offeror. Agencies are released from obligation to protect SBIR data upon expiration of the protection period except that any such data that is also protected and referenced under a subsequent SBIR award must remain protected through the protection period of that subsequent SBIR award. For example, if a Phase III award is issued within or after the Phase II data rights protection period and the Phase III award refers to and protects data developed and protected under the Phase II award, then that data must continue to be protected through the Phase III protection period. Agencies have discretion to adopt a protection period longer than four years. The Government retains a royalty-free license for Government use of any technical data delivered under an SBIR award, whether patented or not. This section does not apply to program evaluation.

(3) SBIR technical data rights apply to all SBIR awards, including subcontracts to such awards, that fall within the statutory definition of Phase I, II, or III of the SBIR program, as described in Section 4 of the SBIR Policy Directive, dated September 24, 2002. The scope and extent of the SBIR technical data rights applicable to Federally-funded Phase III awards is identical to the SBIR data rights applicable to Phases I and II SBIR awards. The data rights protection period lapses only: (i) Upon expiration of the protection period applicable to the SBIR award, or (ii) by agreement between the awardee and the agency.

Copyrights. The awardee may normally copyright and publish (consistent with appropriate national security considerations, if any) material developed with PHS support. The awarding component receives a royalty-free license for the Federal Government and requires that each publication contain an acknowledgement of agency support and disclaimer statement, as appropriate. An acknowledgement shall be to the effect that: "This publication was made possible by contract number _____ from (DHHS awarding component)" or "The project described was supported by contract number _____ from (DHHS awarding component)."

Patents. Small business concerns normally retain the principal worldwide patent rights to any invention developed with Government support. Under existing regulations, 37 CFR 401, the Government receives a royalty-free license for Federal Government use, reserves the right to require the patent-holder to license others in certain circumstances, and requires that anyone exclusively licensed to sell the invention in the United States must normally manufacture it substantially in the United States.

To the extent authorized by 35 U.S.C. 205, the Government will not make public any information disclosing a Government-supported invention for a four year period to allow the awardee a reasonable time to file a patent application, nor will the Government release any information that is part of a patent application.

Information about additional requirements imposed by 37 C.F.R. 401 should be obtained from local counsel or from:

Office of Policy for Extramural Research Administration,
Division of Extramural Inventions and Technology Resources,
National Institutes of Health (NIH)
6705 Rockledge Dr., MSC 7980
Bethesda, MD 20892-7980
(301) 435-0679 (v)
(301) 480-0272 (fax)
jpkim@nih.gov

Inventions must be reported promptly—within two months of the inventor's initial report to the contractor organization—to the Division of Extramural Inventions and Technology Resources, NIH, at the address above. This should be done prior to any publication or presentation of the invention at an open meeting, since failure to report at the appropriate time is a violation of 35 USC 202, and may result in loss of the rights of the small business concern, inventor, and Federal Government in the invention. All foreign patent rights are immediately lost upon publication or other public

disclosure unless a United States patent application is already on file. In addition, statutes preclude obtaining valid United States patent protection after one year from the date of a publication that discloses the invention.

The reporting of inventions can be accomplished by submitting paper documentation, including fax, or electronically through the NIH Edison Invention Reporting System. Use of the Edison system satisfies all mandated invention reporting requirements and access to the system is through a secure interactive Web site (https://s-edison.info.nih.gov/iEdison) to ensure that all information submitted is protected. In addition to fulfilling reporting requirements, Edison notifies the user of future time sensitive deadlines with enough lead-time to avoid the possibility of loss of patent rights due to administrative oversight. Edison can accommodate the invention reporting need of all organizations. For additional information about this invention reporting and tracking system, visit the Edison home page cited above or contact Edison via email at Edison@od.nih.gov.

Sharing Biomedical Research Resources. It is the policy of the NIH that unique research resources developed with NIH funding must be shared with the research community. Restricted availability of these resources can impede the advancement of research. Principles and Guidelines for Recipients of NIH Research Grants and Contracts, as published in the Federal Register Notice on December 23, 1999 (http://ott.od.nih.gov/NewPages/64FR72090.pdf), provide assistance to determine reasonable terms and conditions for acquiring and disseminating research tools, consistent with the objectives of furthering biomedical research and adhering to the Bayh-Dole Act.

(1) Sharing Research Data. See http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html. Offerors shall include in the proposal a plan for data sharing or state why data sharing is not possible.

Reviewers will not factor the proposed data-sharing plan into the determination of scientific merit or score. Program staff will be responsible for overseeing the data sharing policy and for assessing the appropriateness and adequacy of the proposed data-sharing plan.

NIH recognizes that data sharing may be complicated or limited, in some cases, by institutional policies, local IRB rules, as well as local, state and Federal laws and regulations, including the Privacy Rule. As NIH stated in the March 1, 2002 draft data sharing statement (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-035.html), the rights and privacy of people who participate in NIH-sponsored research must be protected at all times. Thus, data intended for broader use should be free of identifiers that would permit linkages to individual research participants and variables that could lead to deductive disclosure of the identity of individual subjects. When data sharing is limited, offerors should explain such limitations in their data sharing plans.

For more information on data sharing, please see our website at http://grants.nih.gov/grants/policy/data_sharing/.

(2) Sharing Model Organisms. NIH is committed to support efforts that encourage sharing of important research resources including the sharing of model organisms for biomedical research (see http://grants.nih.gov/grants/policy/model_organism/index.htm). At the same time, the NIH recognizes the rights of grantees and contractors to elect and retain title to subject inventions developed with Federal funding pursuant to the Bayh Dole Act (see the NIH Grants Policy Statement). Beginning October 1, 2004, all investigators submitting an NIH application or contract proposal are expected to include in the application/proposal a description of a specific plan for sharing and distributing unique model organism research resources generated using NIH funding or state why such sharing is restricted or not possible. This will permit other researchers to benefit from the resources developed with public funding. The inclusion of a model organism sharing plan is not subject to a cost threshold in any year and is expected to be included in all applications where the development of model organisms is anticipated.

Royalties. If royalties exceed $1,500, you must provide the following information on a separate page for each separate royalty or license fee:

1. Name and address of licensor.
2. Date of license agreement.
3. Patent numbers.
4. Patent application serial numbers, or other basis on which the royalty is payable.
5. Brief description (including any part or model number of each contract item or component on which the royalty is payable).

6. Percentage or dollar rate of royalty per unit.
7. Unit price of contract item.
8. Number of units.
9. Total dollar amount of royalties.
10. If specifically requested by the Contracting Officer, a copy of the current license agreement and identification of applicable claims of specific patents (see FAR 27.204 and 31.205-37).

F. PERFORMANCE OF RESEARCH AND ANALYTICAL WORK

In Phase I projects, normally a minimum of two-thirds or 67% of the research or analytical effort must be performed by the small business concern.

In Phase II projects, normally a minimum of one-half or 50% of the research or analytical effort must be performed by the small business concern.

The Contracting Officer must approve deviations from these requirements in writing.

Contractor Commitments. Upon entering into a contract, the contractor agrees, in accordance with the terms and conditions of the contract, to accept certain legal commitments embodied in the clauses of Phase I and Phase II contracts. The following list illustrates the types of clauses to which a contractor is bound. This list is not exhaustive. Copies of complete terms and conditions are available upon request.

Clauses That Apply to Contracts *NOT* Exceeding $100,000

1. ***Standards of Work.*** Work performed under the contract must conform to high professional standards.
2. ***Inspection.*** Work performed under the contract is subject to Government inspection and evaluation at all times.
3. ***Termination for Convenience.*** The Government may terminate the contract at any time for convenience if it deems termination to be in its best interest, in which case the contractor will be compensated for work performed and for reasonable termination costs.
4. ***Disputes.*** Any dispute concerning the contract that cannot be resolved by agreement shall be decided by the contracting officer with right of appeal.
5. ***Equal Opportunity.*** The contractor will not discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin.
6. ***Affirmative Action for Veterans.*** The contractor will not discriminate against any employee or applicant for employment because he or she is a disabled veteran or veteran of the Vietnam era.
7. ***Affirmative Action for Handicapped.*** The contractor will not discriminate against any employee or applicant for employment because he or she is physically or mentally handicapped.
8. ***Gratuities.*** The Government may terminate the contract if any gratuities have been offered to any representative of the Government to secure the contract.
9. ***American-made Equipment and Products.*** When purchasing equipment or products under an SBIR contract award, the contractor shall purchase only American-made items whenever possible.

Clauses That Apply to Contracts Exceeding $100,000

In addition to the foregoing clauses, the following clauses apply to contracts expected to exceed $100,000.

10. ***Examination of Records.*** The Comptroller General (or a duly authorized representative) shall have the right to examine any directly pertinent records of the contractor involving transactions related to this contract.
11. ***Default.*** The Government may terminate the contract for default if the contractor fails to perform the work described in the contract and such failure is not the result of excusable delays.
12. ***Contract Work Hours.*** The contractor may not require an employee to work more than eight hours a day or forty hours a week unless the employee is compensated accordingly (i.e., overtime pay).
13. ***Covenant Against Contingent Fees.*** No person or agency has been employed to solicit or secure the contract upon an understanding for compensation except bona fide employees

or commercial agencies maintained by the contractor for the purpose of securing business.

14. ***Patent Infringement.*** The contractor shall report each notice or claim of patent infringement based on the performance of the contract.

G. ADDITIONAL INFORMATION

1. This solicitation is intended for informational purposes and reflects current planning. If there is any inconsistency between the information contained herein and the terms of any resulting SBIR contract, the terms of the contract are controlling.
2. Prior to award of an SBIR contract, the Government may request the offeror to submit certain organizational, management, personnel and financial information to assure responsibility of the offeror to receive an award.
3. The Government is not responsible for any expenditures of the offeror in advance and in anticipation of an award. In a cost reimbursement contract, reimbursement of costs by the Government may be made only on the basis of costs incurred by the contractor after award and during performance.
4. This solicitation is not an offer by the Government and does not obligate the Government to make any specific number of awards. Awards under this program are contingent upon the scientific/technical merit of proposals and the availability of funds.
5. The SBIR contract program is not intended as a mechanism to invite unsolicited proposals. Unsolicited SBIR contract proposals shall not be accepted under the SBIR program in either Phase I or Phase II.
6. If an award is made pursuant to a proposal submitted in response to this SBIR solicitation, the contractor will be required to certify that he or she has not previously been, nor is currently being, paid for essentially equivalent work by any agency of the Federal Government.
7. Prior to award of a contract, the contractor will be required to provide a Data Universal Numbering System (DUNS) number. A DUNS number may be obtained immediately, at no charge, by calling Dun and Bradstreet at 1-866-705-5711 or via the Internet at https://eupdate.dnb.com/requestoptions/government/ccrreg/. The contractor must also be registered in the Central Contractor Registry (CCR) prior to award of a contract. Registration can be made via the Internet at http://www.ccr.gov.

IX. INSTRUCTIONS FOR PROPOSAL SUBMISSION

A. RECEIPT DATE

The deadline for receipt of all contract proposals submitted in response to this solicitation is:
5:00 p.m., Eastern Time
Monday, November 5, 2007

Any proposal, modification or revision received at the offices designated below after the exact time specified for receipt is “late” and will not be considered unless it is received before award is made, and

1. There is acceptable evidence to establish that it was received at the Government installation designated for receipt of offers and was under the Government’s control prior to the time set for receipt of offers; or
2. It is the only proposal received.

Acceptable evidence to establish the time of receipt at the Government installation includes the time/date stamp of that installation on the proposal wrapper, other documentary evidence of receipt maintained by the installation, or oral testimony or statements of Government personnel.

If an emergency or unanticipated event interrupts normal Government processes so that proposals cannot be received at the office designated for receipt of proposals by the exact time specified in the solicitation, and urgent Government requirements preclude amendment of the solicitation, the time specified for receipt of proposals will be deemed to be extended to the same time of day specified in the solicitation on the first work day on which normal Government processes resume.

Proposals may be withdrawn by written notice received at any time before award. Notwithstanding above, a proposal received after the date and time specified for receipt may be considered if it offers significant cost or technical advantages to the Government and it was received before proposals were distributed for evaluation, or within 5 calendar

days after the exact time specified for receipt, whichever is earlier.

Note: Modifications or revisions to proposals that result in the proposal exceeding the stated page limitations will not be considered.

B. NUMBER OF COPIES

For Phase I, submit the original and 5 copies of each proposal. The Principal Investigator and a corporate official authorized to bind the offeror must sign the original. The 5 copies of the proposal may be photocopies of the original.

For Phase II, see instructions under paragraph VI.

C. BINDING AND PACKAGING OF PROPOSAL

Send all copies of a proposal in the same package. Do not use special bindings or covers. Staple the pages in the upper left corner of each proposal.

X. CONTRACTING OFFICERS AND ADDRESSES FOR MAILING OR DELIVERY OF PROPOSALS

Any small business concern that intends to submit an SBIR contract proposal under this solicitation should provide the appropriate contracting officer(s) with early, written notice of its intent, giving its name, address, telephone, and topic number(s). If a topic is modified or canceled before this solicitation closes, only those companies that have expressed such intent will be notified.

A. NATIONAL INSTITUTES OF HEALTH (NIH)

National Cancer Institute (NCI)

Ms. Mary Landi-O'Leary
Phone: (301) 435-3807
Fax: (301) 480-0309
Email: ml186r@nih.gov

Proposals to the NCI, if mailed through the U.S. Postal Service, must be addressed as follows:

Ms. Mary Landi-O'Leary
Contracting Officer
Office of Acquisitions
National Cancer Institute
6120 Executive Blvd., Room 6044
Bethesda, MD 20892-7193 *

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NCI*.

National Heart, Lung, and Blood Institute (NHLBI)

Mr. John Taylor
Phone: (301) 435-0327
Fax: (301) 480-3338
E-mail: taylorjc@nhlbi.nih.gov

Proposals to the NHLBI, if mailed through the U.S. Postal Service, must be addressed as follows:

Review Branch
Division of Extramural Affairs
National Heart, Lung, and Blood Institute
6701 Rockledge Drive
Room 7091
Bethesda, MD 20892-7924 *

**Change the zip code to 20817 if hand-delivered or delivered by an express or other courier service to the NHLBI.*

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Mr. Matthew L. Packard
Phone: (301) 443-3041
Fax: (301) 443-3891
Email: packardm@mail.nih.gov

Proposals to the NIAAA must be mailed or delivered to:

Mr. Matthew L. Packard
Chief, NIAAA Contracts Management Branch
NIDDK Office of Acquisitions
5635 Fishers Lane
Bethesda, MD 20892-9304 *

**Change the city to Rockville, MD and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NIAAA.*

National Institute on Drug Abuse (NIDA)

Mr. Craig Sager
Phone: (301) 443-6677
Fax: (301) 443-7595
Email: cs591t@nih.gov

Proposals to the NIDA must be mailed or delivered to:

Mr. Craig Sager
Contracting Officer

NIDA R&D Contracts Management Branch
Neurosciences Office of Acquisition
6101 Executive Boulevard
Room 260, MSC 8402
Bethesda, Maryland 20892-8402 *

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NIDA*.

National Institute of Mental Health (NIMH)

Ms. Suzanne Stinson
Phone: (301) 443-2696
Fax: (301) 443-0501
Email: sstinson@mail.nih.gov

Proposals mailed to the NIMH must be addressed to:

Ms. Stephanie Powell
Contract Specialist
Contracts Management Branch
National Institute of Mental Health
6001 Executive Boulevard
Room 8154, MSC 9661
Bethesda, Maryland 20892-9661*

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NIMH*.

B. CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

For general administrative SBIR program questions, contact:

Dr. Denise Burton
Office of Public Health Research (OPHR)
Office of the Chief Science Officer
Phone: (404) 639-4641
Email: DBurton2@cdc.gov

Ms. Susan Clark
Office of Public Health Research (OPHR)
Office of the Chief Science Officer
Phone: (404) 639-4795
Email: sclark@cdc.gov

National Center on Birth Defects and Developmental Disabilities (NCBDDD)

Mr. Carlos M. Smiley
Phone: (770) 488-2754
Fax: (770) 488-2777
Email: CSmiley1@cdc.gov

Proposals to the NCBDDD must be mailed or delivered to:

Mr. Carlos M. Smiley
Contracting Officer
Grants Management Officer
2920 Brandywine Road
Atlanta, GA 30041

Coordinating Office for Terrorism Preparedness and Emergency Response (COTPER)

Mr. Jeffrey L. Napier, MBA, CPCM
Phone: (770) 488-2628
Email: JNapier@cdc.gov

Proposals to COTPER must be mailed or delivered to:

Mr. Jeffrey L. Napier, MBA, CPCM
Chief, Acquisition and Assistance Branch VI
Supporting Terrorism Preparedness, Emergency Response, and Health Information Services
Centers for Disease Control and Prevention (CDC)
Procurement and Grants Office
2920 Brandywine Road, Suite 3111
Atlanta, Georgia 30341-4146

Immunization Safety Office (ISO)

Mr. Jeff Miller
Phone: (770) 488-2651
Fax: (770) 488-2777
Email: afx2@cdc.gov

Proposals to the ISO must be mailed or delivered to:

Mr. Jeff Miller
Contract & Grants Management Specialist
Centers for Disease Control and Prevention (CDC)
Acquisition and Assistance,
Branch B, Team IV
2920 Brandywine Road
Atlanta, GA 30341

XI. SCIENTIFIC AND TECHNICAL INFORMATION SOURCES

Health science research literature is available at academic and health science libraries throughout the United States. Information retrieval services are available at these libraries and Regional Medical Libraries through a network supported by the National Library of Medicine. To find a Regional Medical Library in your area, visit http://nnlm.gov/ or contact the Office of Communication and Public Liaison at publicinfo@nlm.nih.gov, (301) 496-6308.

Other sources that provide technology search and/or document services include the organizations listed below. They should be contacted directly for service and cost information.

National Technical Information Service
1-800-553-6847
http://www.ntis.gov

National Technology Transfer Center
Wheeling Jesuit College
1-800-678-6882
http://www.nttc.edu/

Regional Technology Transfer Centers
1-800-472-6785
http://www.ctc.org/NewFiles/RTTCs.html

XII. RESEARCH TOPICS

NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE (NCI)

The NCI is the Federal Government's principal agency established to conduct and support cancer research, training, health information dissemination, and other related programs. As the effector of the National Cancer Program, the NCI supports a comprehensive approach to the problems of cancer through intensive investigation in the cause, diagnosis, prevention, early detection, treatment, rehabilitation from cancer, and the continuing care of cancer patients and families of cancer patients. To speed the translation of research results into widespread applications, the National Cancer Act of 1971 authorized a cancer control program to demonstrate and communicate to both the medical community and the general public the latest advances in cancer prevention and management.

SBIR Phase I and Phase II awards may not exceed the limits for total costs (direct costs, facilities and administrative (F&A)/indirect costs, and fee) listed under each topic area.

Phase II proposals may only be submitted upon the request of the NCI Contracting Officer, if not submitted concurrently with the initial Phase I proposal under the Fast-Track procedure (described in Section V). Unless the Fast-Track option is specifically allowed as stated within the topic areas below, applicants are requested to submit only Phase I proposals in response to this solicitation.

Advance Notice: SBIR Phase IIB

The National Cancer Institute would like to provide notice of the development of a new SBIR Phase II Award Expansion – entitled the SBIR Phase IIB Bridge. This notice is for informational purposes only and is not a call for Phase IIB Bridge proposals.

Successful translation of SBIR research and technology development into the commercial marketplace faces numerous challenges including significant challenges in regulatory affairs, licensure, commercialization, and production. Prior SBIR Phase II contract awards have encountered difficulties advancing their projects into commercialization. NCI views the SBIR program as a long term effort.

To address these issues, NCI is developing a SBIR Phase IIB Bridge Modification that may provide additional funding of up to $3M and up to three additional years to assist selected and promising small business concerns with their specific hurdles, most notably the FDA regulatory process. Matching private investment funds will be required. Specific proposal requirements including private investment/funds matching of the Phase IIB modification will be provided at the time the Phase IIB proposal is requested by the Contracting Officer.

In order to be eligible for a Phase IIB, contractors must have successfully completed a Phase I award, must have been awarded a Phase II or Fast-Track contract, and, at the discretion of the Government, be invited by the NCI to submit a proposal. Selection decisions for a Phase IIB modification will be based both on scientific/technical merit as well as business/commercialization factors. The Phase IIB modification to the Phase II contract will include the addition and/or removal of phases or tasks in order to advance the R&D effort and to meet the needs of the Government.

NCI Topics:

This solicitation invites Phase I (and in certain topics Fast Track) proposals in the following areas:

229 Development of Molecular Pharmacodynamic Assays for Targeted Therapies

Number of anticipated awards: 6

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $750,000

The NCI requests that qualified small businesses submit proposals to develop pharmacodynamic assays for measuring a number of high-priority molecular targets. (For a list of the targets of interest to NCI, please see: http://sbir.cancer.gov/). The short term goal of this contract is to develop new rigorous, validated assays to measure molecular-level response to treatment in conjunction with preclinical development of new candidate therapeutic agents. These assays should measure modulation of molecular targets upon treatment with investigational anticancer therapeutics and support pharmacodynamic studies in animal models and in human tumor and surrogate tissue samples. Real-time assays that could be used to rapidly assess response to treatment in the clinic in conjunction with a clinical trial are highly desirable. Ideally, these assays should also have a known correspondence to tumor modulation in animal efficacy models for the same target. Standard operating Procedures (SOPs) for these assays must be developed and be provided to the NCI along with all supporting data. (To view sample SOPs, please see: http://sbir.cancer.gov/.)

Small businesses may also submit proposals for the development of assays that measure molecular targets relevant to oncology therapeutics development which have been identified by the small business.

Project goals: The long term goal of this contract is to provide a mechanism to develop a series of molecular pharmacodynamic assays to allow clinical target validation for a wide array of cancer therapeutics to determine earlier in the drug development process if the intended target is modulated and whether this corresponds to either tumor stasis or regression. In addition to the assay itself, the contract recipient will develop and provide to the NCI SOPs that have been fully qualified or validated with human tumor/tissue samples. In addition, the goal is for companies to extend this work into developing research kits or diagnostic agents to stratify patients for clinical trial selection or to evaluate response to new therapeutic agents.

The goal of the NCI SBIR program is to fund small businesses to develop commercially viable products that advance the research and development needs of the Institute. The NCI Strategic Plan identifies validating molecular targets for cancer prognosis, metastasis, treatment response and cancer progression as a strategic priority (Strategy 4.2). Part of this strategy includes creating a library of validated molecular target assays in order to advance broad development of targeted anti-tumor agents. Grant mechanisms thus far have not been an effective method of developing these assays, as they have little publication value. Market analysis indicates that pharmacodynamic assay development is a valuable first step for eventual commercialization of cancer diagnostics and laboratory assays, in addition to serving the needs of cancer therapeutic development.

Two different tracks will be considered:

Track 1 will focus on the development of pharmacodynamic assays for measuring a number of high priority molecular targets. (For a list of the molecular targets of high priority to NCI, please see http://sbir.cancer.gov/.)

This list of molecular targets is being actively pursued by NCI's researchers; thus assays developed under this topic will be good candidates for beta testing at NCI laboratories and clinics. The NCI will determine and periodically re-prioritize the list of molecular targets to be addressed in subsequent years based on the needs of both intramural and extramural investigators.

For Track 2 small businesses are invited to submit proposals for the development of assays that measure molecular targets relevant to oncology therapeutics development which have been identified by the small business.

All proposals will be reviewed by NCI, and overall priority will be given to proposals to develop pharmacodynamic assays of high priority to NCI.

Both tracks will have the following deliverables.

Phase I Activities and expected deliverables:

- Develop a research pharmacodynamic assay for the molecular target described.

- Characterize assay reproducibility, variability and accuracy.
- Deliver to NCI the SOP of the research pharmacodynamic assay for the molecular target described.

Phase II Activities and expected deliverables:

- Develop a qualified or validated molecular pharmacodynamic assay for the target described. The assay should be applicable in the clinical setting.
- Perform studies to characterize the correlation between the resulting assay in tumor versus surrogate tissues (e.g. blood, serum), if applicable.
- Perform studies to characterize the correlation between the resulting assay in human versus animal tissues.
- Make available to NCI all SOPs for this assay.

Fast-Track justification:

While not necessary for all offerors, there are specific situations where fast-track funding would be appropriate and greatly increase the speed of assay development. For example, if the small business recipient has already developed a platform technology for assay development, or similar assays for other molecular targets, the proof of principle can be demonstrated more rapidly.

- Tangible and specific Phase I deliverables that show significant progress toward development of the technology will be required. The following Phase I deliverables will be used as milestones for continued Phase II funding:
  - The SBIR recipient must deliver research assay SOPs within 3-6 months.
  - Demonstrate acceptable real-time assay performance in animal tumor tissue.
- Before any Phase II funding is awarded, the contract manager must receive both of the tangible milestones written above and verify that the research conducted and SOPs are complete and accurate. Once verified, the contract manager may approve additional Phase II funding.

236 Antibody Array for Cancer Detection`

Number of anticipated awards: 3-5

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $1,000,000

The purpose of this initiative is to develop high throughput antibody arrays for quantitative analysis of multiple biomarkers for early detection and diagnosis of cancer. These arrays may include antibodies based on the applicant's own research and knowledge of the literature. Applicants are also encouraged to contact extramural investigators from the NCI's Early Detection Research Network (EDRN; www.cancer.gov/edrn), which is developing a number of biomarkers for cancer detection, diagnosis and prognosis. Please contact one of the members or associate members at: http://edrn.nci.nih.gov/memberslist/x.xml. The selected applicants will develop microarrays, the chemistry of which may be based on nanotechnology and/or microfluidics. Applicants should focus initial development on the diagnosis and early detection of prostate, breast, lung, colon, and other major epithelial cancers. In Phase II, the antibody microarray developed in Phase I will be validated under a plan developed with the NCI project officer. Applicants are encouraged (but not required) to develop a validation plan that includes the participation of EDRN investigators. It is anticipated that such participation will result in accelerated development, production, validation and commercialization of antibody microarray technology for early detection and diagnosis of cancer.

Project goals:

- Prepare and purify biomarker-specific antibodies in the form of recombinant antibodies or monoclonal antibodies (mAb) and construct arrays.
- Develop and/or improve methodologies for quantitative measurements of the bound antigens on Ab microarrays.
- Perform analytical validation, e.g., test the reproducibility, sensitivity, specificity and dynamic range of detection in collaboration with EDRN and other institutions to measure the efficacy of the developed array.

Currently, there is no single marker or a combination of biomarkers that has sufficient sensitivity and specificity to diagnose early stage cancer. However, recent developments in gene and proteomic profiling of precancerous and cancerous lesions suggest that a combination or a patterns of markers may be used to distinguish between cancer and non-cancer with high sensitivity and specificity (95-100%). Innovative technologies, such as microfluidics and nanotechnology, combined with antibody arrays are likely to provide a reliable, sensitive and quantitative detection tool for measuring differentially expressed biomarkers from a limited amount of sample (20ul or less of serum). The involvement of small businesses through the SBIR contract mechanism will strengthen the EDRN's efforts in the development, validation and commercialization of biomarkers for early detection and risk assessment.

The work performed under this contract is between a selected Biotech Company and EDRN Investigator/s and the NCI EDRN Program staff. Unless otherwise agreed to in writing between the selected Biotech Company and the institutions of the EDRN, the following will guide the Intellectual Property management and sharing of research resources generated from the work performed under this contract. All inventions conceived or first actually reduced to practice solely by the selected Biotech Company investigators under this Agreement will be the property of the selected Biotech Company in accordance with 35 USC Section 200, et. seq., subject to any intellectual property (IP) rights of the providers of biomarkers (e.g., institutions of EDRN investigators) to the selected Biotech Company. All inventions conceived or first actually reduced to practice jointly by the selected Biotech Company and any EDRN Investigators or NCI EDRN program staff will be jointly owned by the inventors' institutions. The Selected Biotech Company agrees that it will permit EDRN Investigators to use such inventions under terms consistent with the *Principles for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical research Resources* (http://grants.nih.gov/grants/intell-property_64FR72090.pdf).

The providers of biomarkers will retain their respective IP rights for those biomarkers developed by their institution's respective investigators. The selected Biotech Company is responsible for negotiating access rights, including any commercial license rights, to all materials provided to the selected Biotech Company, and any related IP, in order to conduct the activities funded under this Agreement.

NCI, EDRN Investigators and the EDRN Data Management and Coordinating Center, managed by the Fred Hutchinson Cancer Research Center ("EDRN DMCC") will have unlimited rights as defined in FAR 52.227-14, general to the following data developed during the course of this project: (i) protocols for using the antibody microarrays to be developed by the selected Biotech Company and individual antibodies independent of the antibody arrays; (ii) initial research results concerning the use of antibodies against specimens provided by EDRN Investigators; (iii) antibody characterization data, including the results of testing to demonstrate the utility of particular antibodies; and (iv) validation data based on subsequent experiments involving the antibody microarrays.

Authorship of publications resulting from data developed under this contract will be shared by all contributing parties including the NCI.

Phase I Activities and expected deliverables:

Relevant biomarkers could be selected from published literature or by contacting one of the EDRN extramural investigators. (Please contact one of the members or associate members at: (http://edrn.nci.nih.gov/memberslist/x.xml.)

- Establish the proof of principle.
- Develop an antibody microarray for detection of 3 biomarkers using innovative technologies.
- Demonstrate that the tiled antibodies perform as well or better than a conventional ELISA in the detection of these biomarkers in serum from cancer patients.

Phase II Activities and expected deliverables:

Applicants are encouraged (but not required) to develop a validation plan that includes the participation of EDRN investigators.

- Develop antibody microarrays with a capability to simultaneously detect and measure the concentration of 30-50 biomarkers. These arrays can include both biomarkers from the EDRN as well as biomarkers identified by the small business.

- Validate antibody microarrays in high-risk subjects.
- Produce and test up to 1000 microarrays with samples from normal and case subjects.

241 Multifunctional Therapeutics Based on Nanotechnology

Number of anticipated awards: 3-5

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $1,000,000

Nanoscale delivery platforms carrying therapeutic payloads and delivered within close proximity of the tumor *in vivo* can play a significant role in increasing the effectiveness of the treatment while decreasing the severity of side effects. Such techniques would be highly relevant, particularly, for organs that are difficult to access because of a variety of biological barriers, including those developed by tumors. For example, nanoparticles are capable of crossing the blood-brain barrier due to their small size and thus are an excellent candidate for non-invasive treatment of brain tumors.

Multifunctional nanoparticles, which are currently emerging, allow for a combination of an imaging agent with a therapeutic as a reporter of therapeutic efficacy in the same package. In conjunction with the development of these devices, local targeting techniques are emerging. This process can utilize specific epitopes expressed on tumor cells or other cellular markers of biological processes such as angiogenic and apoptotic pathways. In molecular oncology, this is potentially useful as a general approach since it allows for targeting of multiple cancers or more broadly for targeting of multiple diseases. For instance, there are already examples of multi-functional nanoparticles that target vascular peptides, growth factor receptors, transmembrane proteins such as ion channels, and are utilized for both cancer and cardiovascular disease recognition.

To accelerate such efforts, the National Cancer Institute (NCI) requests proposals for the development of commercially-viable nanotechnology-based multifunctional therapeutics (designed to deliver chemotherapeutics to cancerous cells while sparing normal, healthy tissue), leading to increased therapeutic index and improved patient outcomes.

Project goals:

The goal of this project is to develop an *in-vivo* nanoparticle-based delivery platform with improved efficacy as compared to currently used treatments. For example, these devices can take the form of multi-functional nanoparticles carrying encapsulated drugs. The platforms may also utilize imaging agents for a combination of therapeutic and diagnostic modalities that aim to provide real-time feedback and monitoring of therapy. To increase commercial success, it is highly recommended that the nanoparticle system be administered orally or systemically, rather than intratumoral implantation. They may include, but are not limited to the following:

- novel therapeutic nanoparticles
- novel tumor targeting and concentrations schemes
- novel drug loading and releasing schemes
- novel nanoparticles able to cross the blood-brain barrier.

Phase I Activities and expected deliverables:

- Demonstration of targeting and/or concentration techniques for a specific organ/disease.
- Proof of concept small animal studies showing improved therapeutic efficacy as compared to the use of free drug.
- Fabrication techniques resulting in the manufacturing of nanoplatforms with good reproducibility should be developed. The novel use of existing particles acquired from the commercial manufacturer will also be considered under this program.

Phase II Activities and expected deliverables:

- *In vivo* small animal drug efficacy demonstration (at least 60 day study with statistically relevant number of animals) utilizing an appropriate animal model.
- Long-term toxicity studies (biodistribution and bioelimination for IV administered nanodevices and biocompatibility for implanted devices).

- Nanoplatform manufacturing and scale-up activities.
- IND-enabling studies carried out in a suitable pre-clinical environment
- Initiation of large animal studies

242 Biosensors for Early Cancer Detection and Risk Assessment

Number of anticipated awards: 3

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $1,000,000

A primary cause of poor survival rates from cancer is that many cancers are detected late, after they have spread or metastasized to distant sites. For most types of cancer, the earlier the detection the greater the chances of survival. For example, when colorectal cancer is detected in its earliest stages, the 5-year survival rate is as high as 95%, but if detected after it has spread, the survival rate is less than 10%. Five year survival rates for cancers where screening tools are available are 4-6 times greater than for cancers for which there are no viable screening tools. However, even for cancers where screening tools currently exist, there is room for improvement in the accuracy of the tests or in making them more acceptable to patients. Consequently, there is a need to develop methods to noninvasively and accurately detect cancers at early stages of development and to determine those individuals at increased risk of developing cancer. Given the heterogeneity of transformed cells found in many tumors, it is unlikely that a single biomarker will be able to provide sufficient sensitivity and specificity to be useful as an early detection screening assay. Thus, there is a need for devices that can accurately and reproducibly measure multiple cancer biomarkers or circulating tumor cells in bodily fluids or other specimens obtained by minimally invasive methods. As these biomarkers or tumor cells are likely to be present in low abundance, the device must be very sensitive. Biosensors have the potential to fulfill this need.

Project goals:

The purpose of this solicitation is to develop biosensors for early cancer detection and risk assessment. Biosensors are bioanalytical devices that combine biochemical recognition or binding elements, physicochemical transducers, and readout modalities. Biochemical recognition elements include antibodies, proteins and peptides, nucleic acids, aptamers, cell receptors, enzymes, and tissues. The transducer may be optical, electrochemical, thermometric, piezoelectric or magnetic. Biosensors for early cancer detection and risk assessment have potential advantages over other analytical methods including the capability for multi-target analyses, automation, speed, flexibility and reduced costs. Given the complexity of biological specimens, it may be necessary to incorporate front end sample preparation.

Phase I activities and expected deliverables:

- Design novel biosensors or improve existing biosensor technologies that can be used either to measure physiological concentrations of multiple known biomarkers for early cancer detection or risk assessment or to capture and measure circulating tumor cells.
- Perform analytical validation (e.g., accuracy, reproducibility, sensitivity, specificity and dynamic range) using purified samples in an artificial matrix that mimics the clinical specimens.
- Demonstrate flexibility to allow measurement of new biomarkers to be incorporated or substituted as they become available.

Phase II activities and expected deliverables:

- Complete the development and automation of the biosensor and demonstrate its speed, flexibility, and ability to reduce costs.
- Perform analytical validation (e.g., accuracy, reproducibility, sensitivity, specificity and dynamic range) using appropriate patient specimens (e.g., urine, sera, plasma, or sputum).
- Determine clinical sensitivity and specificity.

243 Novel and Improved Methods to Measure Cancer Epigenetic Biomarkers

Number of anticipated awards: 3-6

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $1,000,000

Epigenetic markers, especially DNA methylation, have shown promise for early detection of cancerous lesions. However, it is unlikely that any single epigenetic marker has sufficient sensitivity and specificity to accurately and reliably detect early cancers or to predict cancer risk. Also, methods used to measure DNA methylation and other epigenetic markers need to be improved to increase specificity, sensitivity, reproducibility, and throughput. For example, most methods to measure CpG methylation at specific sites require bisufite treatment, which is time consuming, can result in incomplete conversion of cytosines to uracils, and can cause fluctuations in methylation measurements, thus decreasing accuracy. Assays, methods and arrays or chips need to be developed to integrate and improve the use of DNA methylation as a non-invasive approach for early cancer detection and risk prediction.

Project goals:

The purpose of this initiative is to solicit small businesses to develop innovative and improved assays, methods, or chips for detecting CpG methylation status for early cancer detection and risk assessment. This SBIR contract solicitation encourages: (1) development of new methods for methylation detection that do not require bisulfite treatment; (2) development of methods that substantially increase the conversion rate of cytosine to uracil by bisulfite treatment; (3) development of a chip for detection of methylation biomarkers; and (4) development of more sensitive techniques that allow for DNA methylation to be measured in small volumes of bodily fluids such as sera or sputum. Most current methods require large volumes, making them unsuitable for use with these bodily fluids and hence for use in early cancer detection.

Phase I activities and expected deliverables:

Develop innovative and improved methylation detection methods that do not require bisulfate treatment, or that substantially increase the conversion rate of cytosine to uracil by bisulfate treatment, to allow for the quantitative measurement of CpG methylation and/or an increase in analytical sensitivity:

- Demonstrate proof of principle for the development of chips.
- Demonstrate feasibility by testing a panel of 5 to 10 genes.
- Test the usefulness of these methods using DNA extracted from cell lines or clinical samples.

Phase II activities and expected deliverables:

Refine and analytically validate the assays, methods, or chips to test accuracy.

- Use these assays, methods, or chips to test the methylation status for more than 30 genes.
- Validate the sensitivities and specificities of the assays and methods using appropriate clinical samples.
- Plan the next step for commercialization of the assays, methods, and chips for detecting epigenetic biomarkers.

244 High Throughput Assays for Isolation and Characterization of Cancer Stem Cells

Number of anticipated awards: 3-5

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $1,000,000

Cancer Stem Cells (CSC), represent a small population of cells within a tumor, which drives growth and metastasis, and has the phenotypic properties of stem cells. While chemotherapy and radiation therapy are able to eradicate most of the tumor cells, especially the fast dividing cells, these treatments frequently fail in eradicating the CSC, which might be dormant for years. Eradication of the CSC is thought to be essential for cure.

Currently the identification and isolation of CSC is based on markers that are shared by the same tissue stem cells and occasionally by other cells as well. This is followed by functional assays such as spheroid formation by cancerous cells in vitro for some cancer cells such as breast, prostate and brain, and by the recapitulation of the original tumor by the cancer stem cells in vivo in NOD SCID mice. There is an urgent need for the development of high-throughput assays for the isolation and characterization of cancer stem cells, particularly from premalignant and early stage cancers, as well as from exfoliated cells (e.g., urothelial cells in urine

sediment) to improve early detection, diagnosis and prognosis.

Project goals:

- Select a panel of differentially expressed markers for CSC.
- Develop affinity reagents to target the differentially expressed markers in the form of monoclonal antibodies or recombinant antibodies, RNA or DNA aptamers, or small chemical molecules.
- Develop high-throughput assays and methods for reproducible analysis of CSC.
- Perform analytical validation, e.g., test the reproducibility, sensitivity, specificity in comparison with the current assays.
- Test the utility of the developed assay in identification and isolation of CSC from premalignant lesions (e.g., DCIS, or HGPIN), early stage cancers and exfoliated cells of cancer patients (e.g., colon, bladder, breast, lung pancreas, and head and neck).

Phase I activities and expected deliverables:

- Establish the proof of principle: Demonstrate that the developed assay, based on a panel of differentially expressed markers, can detect cancer stem cells at least as well as the current methodologies and functional assays or better.
- Demonstrate that the same cancer stem cells can be isolated from the original cancer, the premalignant lesion and the exfoliated cells (e.g., for colon cancer).

Phase II activities and expected deliverables:

- Validation of the assay: High-throughput isolation of cancer stems cells from: (1) 50 cancer patients with premalignant lesions (e.g., DCIS, HPIN); (2) 50 cancer patients with exfoliated (e.g., urine sediment of bladder cancers) cells;
- Testing the utility of the developed cancer stem markers for early detection, diagnosis and prognosis.

245 Assay Systems for Drug Efficacy in Cancer Stem Cells

Number of anticipated awards: 4-6

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $1,000,000

Cancer stem cells (CSC) are central to tumor development. Although research on CSC is currently in the discovery phase, the clinical potential of CSC is becoming more apparent. Evidence for the presence of CSC has been found for a number of tumor sites, including brain, breast, colon and leukemia. CSC are self-renewing, able to give rise to a xenograft tumor from a single cell, and able to recapitulate all cell types in the resultant tumor. Interaction of CSC with their microenvironment (niche), including their response to signals from specific cell types, supports cancer development.

Although CSC identification is currently very early in its development, the universality of CSC occurrence in cancer is an accepted fact. It is, therefore, fair to assume that CSC are present at all stages of cancer development enabling a paradigm shift toward the control of CSC in a “prevention mode”. The fact that the number of CSC may be limited in individuals predisposed to cancer, or in early lesions or in lesions at risk for recurrence, may be an advantage for preventive intervention, as is the much greater accessibility compared with site-contained or malignant cancers. The observations that CSC are presumed to be largely quiescent and, therefore, exist in a “pseudo-synchronized state” should be of benefit as well. For example, preventive intervention approaches should enable the use of “synthetic lethality” wherein “pseudo-synchronized” CSC populations in early cancers are induced to proliferate, followed by chemopreventive modalities. Potential chemopreventive modalities for the treatment of CSC may include use of minimally toxic differentiation agents, anti-inflammatory agents, anti-angiogenic agents, and transgenes, applied topically or systemically, whether individually or in combination.

Eradication of CSC is thought to be essential for cancer control. Current therapies are able to eradicate rapidly dividing tumor cells in some cases, but these treatments frequently fail to eradicate CSC, resulting in tumor recurrence. CSC are few in number, estimated at between 0.1%-5% depending on tumor type and stage of development, appear to

be largely quiescent, and are enriched for the ATP-binding cassette (ABC) drug resistant genes. These attributes would, presumably, reduce the ability of many anti-cancer drugs to control CSC. Understanding of CSC resistance to current therapies should lead to the development of new strategies, including the identification of relevant molecular targets for cancer prevention.

Project goals:

- Establish CSC-based assay systems in vitro.
- Establish CSC-based assay systems able to monitor drug toxicity and efficacy in vitro.
- Establish CSC-based assay systems in vivo.
- Establish CSC-based assay systems able to monitor drug toxicity and efficacy in vivo.
- Develop high-throughput CSC-based assay systems in vitro.
- Develop high-throughput CSC-based assay systems able to monitor drug toxicity and efficacy in vitro.
- Investigate the effect of a select number of potential agents viz. CSC systems, both in vitro and in vivo, to demonstrate reproducibility, sensitivity, and specificity.
- Validate the in vitro and in vivo CSC-based assay systems as appropriate for commercialization of the assays.

Phase I activities and expected deliverables:

- Establish CSC-based assay systems able to monitor drug toxicity and efficacy in vitro.
- Develop high-throughput CSC-based assay systems able to monitor drug toxicity and efficacy in vitro.

Phase II activities and expected deliverables:

- Continue to pursue Phase I activities.
- Establish CSC-based assay systems able to monitor drug toxicity and efficacy in vivo.
- Investigate the effect of a select number of potential agents viz. CSC assay systems, both in vitro and in vivo, to demonstrate reproducibility, sensitivity, and specificity.
- Validate the in vitro and in vivo CSC-based assay systems as appropriate for commercialization of the assays.

246 Integrating Patient-Reported Outcomes in Hospice and Palliative Care Practices

Number of anticipated awards: 3

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $1,000,000

Project duration: Phase I: 9 months; Phase II: 2.5 years

Numerous reports have identified the need to improve the management of symptoms and health-related quality of-life (HRQOL) problems in cancer patients whether these problems are related to treatment or the course of disease. This need is particularly great for cancer patients who suffer from pain and other significant symptoms, or who are at the end of life. Cancer patients falling into these categories, furthermore, are often and increasingly cared for not exclusively by oncology specialists, but by health care professionals specializing in hospice and palliative medicine. This presents both promises and challenges for pain and symptom management, since it adds to the number, complexity, and settings of the interactions between patients and various health care providers. Effective collection and communication of data on patients' symptoms and deficits in HRQOL becomes an even more critical challenge in such a system. For example, the fact that most of the care delivered by hospices to dying patients occurs in their homes, heightens the need for effective ways to assess symptoms and to make such data available to health care providers in a timely manner.

Addressing this issue, the short-term goal of this project requires the offeror to develop integrated, ongoing patient-reported outcome (PRO) assessment methods to provide timely, efficient, individualized information for monitoring patient progress and improving decision making in the hospice and palliative care setting. The long-term goal is to develop computerized PRO data measurement and information systems for use by clinicians and patients. Such systems would

measure cancer-specific symptoms and HRQOL domains using well-validated instruments as well as methodologies such as item banking and computer adaptive testing administration, in order to gather patient-reported data for use in clinical practice. The systems would also ideally provide decision support for clinicians, and be integrated with electronic health records across various health care providers (e.g., hospice and palliative care clinicians, oncologists) and settings (home, inpatient hospice, nursing home, clinic, hospital). The goal of this project is to develop a measurement and information system that specifically addresses the unique challenges raised in pain and symptom management and the care of dying patients, and meets the needs of health care professionals in various settings where hospice and palliative care patients receive care.

Such systems are intended to facilitate collection of information from patients via alternative assessment media platforms, such as telephones, computers, handheld devices, and the Internet at selected or patient-determined intervals (not only at the time of a patient visit). Health status reports for both patients and clinicians need to be screened for urgency and tailored to their preferences and knowledge in a standardized format that can be integrated with medical records data, evidence-based guidelines, and resources for responding to patient needs. Data collection that meets privacy and confidentiality concerns will be used not only for patient care, but also to develop norms for clinician use and for research.

The systematic use of PRO information to guide care is accepted by clinicians in theory but does not occur in routine oncology practice in the U.S. (Donaldson, M.S., “Taking Stock of Health-Related Quality of Life Measurement in Oncology Practice in the United States,” 2004, JNCI). Although much methodological instrument development has occurred, and feasibility studies collecting data in conjunction with the patient visit have shown improved patient-clinician communication, many challenges to widespread adoption still exist. These challenges include general clinician belief that instruments are not adapted for efficient use at the individual (rather than clinical trial) level. The use of HRQOL in routine practice requires acceptance by clinicians, patients, and administrators, timely communication among all who provide care, efficient data collection, analysis, and reporting and resources for responding to identified patient problems. For patients, it will require addressing the acceptability of PRO assessment in light of response burden and possible concerns about confidentiality. Importantly, patients will expect that data they provide will help to improve their care. The way forward, however, does not lie simply in adding PRO measurement to other clinician tasks such as the occasional, time-limited patient visit. Rather, effective implementation will require new information infrastructures and technologies to embed the timely, routine use of PRO information in the care process. In particular, a key objective is to uncouple outcomes measurement from the strictures of the patient visit—an opportunity provided by information technologies.

The rapid deployment and public acceptance of information technologies and networks offer an opportunity for developers to incorporate information about patient functioning with clinical records. Such systems would provide as-needed reports to patients and treating clinicians to assist in informed decision-making to improve health care. Health status reports can be tailored to the preferences and knowledge of the patient and clinician and may include graphical display of health status over time as well as identifying the need for clinical attention. Clinicians may wish to respond by e-mail, phone, or other means, rather than by patient visit only. Such tracking may help patients become more involved with their own care as do dieters who keep food records. This may also serve as a useful aid for caregivers to have a systematic and standardized way to monitor their loved ones health status and convey this information to the healthcare providers.

The NIH RoadMap initiative to develop the Patient-Reported Outcomes Measurement Information System (PROMIS) is in the process of developing item banks to capture a range of symptoms (e.g., pain, fatigue, depression, sleep/wake function) and HRQOL (e.g., physical function) for a broad range of chronic diseases (http://www.NIHpromis.org/). The PROMIS may serve as a valuable source for standardized measures, however there may be domains not captured by the system that are of importance in palliative and end-of-life care settings. There is need to act now to work with patients and hospice and palliative medicine clinicians to develop and test integrated information systems that focus on pain and symptom management and end-of-life care, and implementation in hospice and palliative care settings so that products like the PROMIS initiative can be successfully incorporated into practice. Such systems could then be disseminated into larger practice settings (e.g., general oncology) in which pain and symptom management are critical

but provided by a broader variety of clinicians in diverse practice settings.

The ideal system should be adaptable to integrate with other data systems and be platform-independent (work across Windows, Mac, Unix, and other operating systems). PRO administration should be device independent, allowing patients to self-report via devices such as telephone, Internet, or handhelds. A flexible self-report system gives patients the freedom to choose a device that meets their preferences, schedule, or limitations. Opportunities for proxy report by caregivers when the patient is too ill to respond should be considered.

PRO data can be integrated with clinical information and reports tailored to user preferences, to serve a variety of key clinical functions. For hospice and palliative care clinicians, the report can profile patient functioning over time with clinically meaningful changes in health status highlighted for their attention. Such reports can include links to clinical practice guidelines and treatment recommendations adapted for the individual patient, local practice, and available resources. More active forms of clinical decision support may also be integrated within these systems—e.g., through use of care algorithms or care quality measures that utilize clinical data captured on individual patients. The PRO data collection system may be used to facilitate communication between different members of the health care team (e.g., various physicians, nurses, allied professionals). Data may also be used to provide feedback for patients in the form of reports that can be displayed in a format that is easily understandable for them to monitor their own progress and to indicate when they may need immediate care. De-identified PRO and clinical data could foster a better understanding of patterns of care and treatment effectiveness as well as to track changes in special populations and across tumor sites. Further, data could be used to update the data collection instruments to improve questionnaire properties and for clinical research.

NOTE: The National Cancer Institute (NCI) promotes the use of state-of-the-art media technology to develop tools, interventions, programs and systems that 1) are needed by professionals or the public to reduce cancer risk or improve the quality of life of cancer survivors; 2) help fill gaps in research; 3) resolve barriers to use so that products can be used effectively in medical and community settings; and 4) improve communication behaviors between primary care professionals and patients/care-givers in cancer-related matters.

Phase I activities and expected deliverables:

- Conduct interviews, focus groups, clinical site visits and meetings among patients, clinicians, hospice and palliative care personnel, and information technology and PRO experts to identify local needs and formulate an approach to developing and implementing a PRO assessment system.
- Perform literature reviews to determine the scientific and technical feasibility of creating and implementing such systems in practice settings, focusing on various key components of these systems (e.g., PRO assessment media, PRO assessment methodology, electronic health record infrastructure, provider communication media and systems, clinical decision support systems);
- Provide a report detailing the program design and specification including a plan to integrate the PRO information system into a network of clinical practices;
- Develop a working prototype of the PRO data monitoring, collection, and reporting infrastructure;
- Include in the proposal, letters of agreement from organizations participating in Phase I feasibility testing and evaluation.
- Obtain letters from interested participants for Phase II testing and evaluation.
- Present Phase I findings and demonstrate the final prototype to an NCI Evaluation Panel.

NOTE: Offerors are required to fully develop their individual product in Phase II to meet the goals of this SBIR contract topic. Where feasible and appropriate, Phase II contractors may be required to collaborate, coordinate, or communicate with other NCI funded contractors or programs. Offerors are also required to develop a dissemination package that enhances marketability.

Phase II activities and expected deliverables:

- Develop and integrate the information systems in clinical practices, focusing on key components.

- Create evaluation measures.
- Evaluate and refine the program based on user feedback.
- Create a manual, tutorial, and other educational materials designed to integrate this system in other clinical practices including cancer centers and community care settings—addressing both technical implementation and social/cultural change management.
- Developed software to run the system and track outcomes.
- In the first year of the contract, provide the program and contract officers with a letter of commercial interest.
- In the second year of the contract, provide the program and contract officers with a letter of commercial commitment.
- Include $24,000 in the budget for evaluation of the product at NCI's Evaluation Lab.
- Present final research findings and demonstrate the final product at an NCI/DCCPS sponsored Product Showcase.
- Prepare at least one manuscript describing the development and evaluation of the product for publication in a peer-reviewed scientific journal.
- Submit final report in the template provided by the NCI program officer.

247 Portable e-Technology Diet and Physical Activity Tools for Consumers

Number of anticipated awards: 3

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $1,000,000

Project duration: Phase I: 9 months; Phase II: 2.5 years

The short-term goal of this project is to develop a prototype of an innovative portable assessment and intervention tool for energy balance (integrative diet and physical activity), and a website prototype for monitoring the work accomplished with this tool. The portable e-technology tool envisioned will incorporate both self-report and "objective" [e.g., motion detection, tracking vital signs, analysis of physiology, GPS, digital camera, etc.] indicators. The portable e-technology tool needs to be marketable to individuals (i.e., consumers) interested in physical activity, diet, and/or weight loss behavior change, as well as, to health researchers. The long-term goals are to 1) develop and evaluate the portable e-technology tool and an interactive network platform that integrates the tool and 2) develop a tracking component for the network.

Rates of obesity in the United States have dramatically increased over the past 20 years to reach epidemic levels. Obesity, the result of energy imbalance (i.e., energy intake/energy expenditure), has been linked to several types of cancer (IARC, 2002). Physical inactivity and unhealthy diets, key contributors to obesity, have been designated as key areas of interest at NCI (e.g., 2008 Bypass Budget), NIH (e.g., trans-NIH obesity task force), and DHHS (Health People 2010). During an NCI-sponsored working group meeting, entitled "Capturing Physical Activity and Diet in Real Time", the need for innovative tools to assess and modify obesity related health behaviors was highlighted by the expert panel.

Currently, research on interactive and/or simultaneous effects of energy intake and expenditure is sparse (IARC, 2002). Instead, research has focused on physical activity, diet, and weight separately in relation to cancer (as well as other health outcomes). As a result, the development of portable e-technology tools that adequately capture real-time energy balance in an integrated and verifiable manner has lagged.

To better understand the influence of energy balance on cancer and cancer prevention, the development of portable e-technology tools to precisely measure and modify energy balance-related health behaviors (i.e., diet, physical activity) is critical. Current tools (e.g., surveys, handheld computers, cell phones, accelerometers, etc.) have not been developed with the dynamic (i.e., real time) and integrative nature of energy balance in mind. Furthermore, there has been limited integration of the self-report and "objective" methodologies to understand and modify energy balance. There also exists a need to assess and modify diet and physical activity among groups at high risk of obesity and cancer, namely ethnic minorities, socio-economically disadvantaged groups, and low literate populations.

Interdisciplinary collaborations (e.g., behavioral researchers, computer scientists, nutrition specialists, exercise physiologists, health disparities scientists, etc.) are required to move the field forward in an integrative manner.

In addition to the need to develop portable e-technology tools that integrates different aspects of energy balance, there is also a need to consolidate the information obtained from these portable e-technology tools into an interactive database that can be monitored and tracked over time. To date, consumers and researchers have typically used basic portable tools for particular behaviors (e.g., diet) in isolation of a centralized database, which limits the potential dissemination and interdisciplinary use of the information. An interactive database can provide a centralized channel for individuals to easily self-monitor multiple health behaviors, for information to be analyzed and potentially send in appropriate form back to the individual, and for researchers to engage in creative interdisciplinary collaborations with multi-levels of longitudinal data collected in real-time.

NOTE: The National Cancer Institute (NCI) promotes the use of state-of-the-art media technology to develop tools, interventions, programs and systems that 1) are needed by professionals or the public to reduce cancer risk or improve the quality of life of cancer survivors; 2) help fill gaps in research; 3) resolve barriers to use so that products can be used effectively in medical and community settings; and 4) improve communication behaviors between primary care professionals and patients/care-givers in cancer-related matters.

Phase I Activities and expected deliverables:

- Develop a prototype of a portable e-technology tool that can assess diet and physical activity using both self-report and “objective” methods.
- Convene focus groups or conduct interviews with potential end-users of the system to determine if the system contents, format, etc. are appropriate for ease of use.
- Develop real-time or just-in-time information feedback options to the consumer in all developed portable e-technology tools.
- Provide outlines for an operation manual and primer for both consumer and researcher tools.
- Develop software designs and specifications, where applicable.
- Develop a working prototype of an interactive web-based platform for consumers and researchers.
- Include in the proposals, letters of agreement from organizations participating in Phase I feasibility testing and evaluation.
- Obtain letters from interested participants for Phase II testing and evaluation.
- Present Phase I findings and demonstrate the final prototype to an NCI Evaluation Panel.

The integrative, portable, e-technology tool could enhance existing technology (e.g., handheld computers, cell phones, text message devices, accelerometers, electronic pedometer, heart rate monitors, GPS, interactive voice recognition, bar scanning, etc.), merge existing technology, or develop a new platform. The portable tool needs to be user-friendly to individuals from disadvantaged backgrounds (e.g., ethnic minorities, low SES groups, and individuals with low literacy). Consultation with leading behavioral researchers with expertise in diet, physical activity, and weight is required in the development of the tool. Usability testing with consumers and researchers is required during the Phase I.

NOTE: Offerors are required to fully develop their individual product in Phase II to meet the goals of this SBIR contract topic. Where feasible and appropriate, Phase II contractors may be required to collaborate, coordinate, or communicate with other NCI funded contractors or programs. Offerors are also required to develop a dissemination package that enhances marketability.

Phase II Activities and expected deliverables:

- Develop and beta-test an integrative, portable, e-technology tool(s) and web site(s) with individuals from different population groups, and with researchers.
- Evaluate and refine the program based on user feedback.

- Developed software to run the tool(s) and track outcomes.
- Develop the final portable tool(s), website(s), and related software package(s) where applicable.
- Develop related operations manuals and primers, addressing both technical implementation and social/cultural change management.
- In the first year of the contract, provide the program and contract officers with a letter of commercial interest.
- In the second year of the contract, provide the program and contract officers with a letter of commercial commitment.
- Include $24,000 in the budget for evaluation of the product at NCI's Evaluation Lab.
- Present final research findings and demonstrate the final product at an NCI/DCCPS sponsored Product Showcase.
- Develop at least one article describing the development and evaluation of the portable e-technology tool and web site that is suitable for publication in scientific venues.
- Submit final report in the template provided by the NCI program officer.

248 Patient-Centered Coordinated Cancer Care System

Number of anticipated awards: 3

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $1,000,000

Project duration: Phase I: 9 months; Phase II: 2.5 years

The goal of this project is to develop an automated care coordination program that will 1) allow all cancer care team members to view and participate in the coordination of cancer care during the diagnostic process, 2) assist patients in seeking needed evaluation of an abnormality, and 3) track relevant patient health status, outcomes data, symptom management recommendations, and decision points in real time and in full view of the patient and care team. This represents a slight modification of the 2006 version of this contract topic that focused on the palliative care process rather than the diagnostic process.

The 2006 version of this SBIR topic focused on using the Veteran's Health Administration VHA's electronic medical record (VISTA) as an infrastructure to which mobile technology linked care coordinators and patients managing cancer symptoms and pain.(2007,2002) Access to community resources, coordination of communication among providers, and the facilitation of dialogue during an evolving stage of care were all requirements underlying implementation of this mobile technology and were addressed in the first version of this SBIR initiative to replicate the VHA's symptom management technology for use in the community. The requirements address care needs at many points in the Cancer Care Continuum.(2003) For example, VISTA has shown promise for the effective management of primary care patients and implementation of cancer screening in populations served by Federally Qualified Health Centers (FQHC) but the coordination of community resources, and communication among providers are critical needs during the diagnostic process as well.(2003,2005,2006) This current topic builds on the experience with the symptom management and Vista system and FQHCs to provide patient-centered bridging technology that gives patients the information they need, when they need it so they can successfully navigate through the diagnostic process between an abnormal cancer screening test or symptomatic presentation and its resolution as a benign abnormality or a cancer diagnosis.

Of the1,358,030 new cancer cases in the US in 2005 (2005), a disproportionate burden was borne by the uninsured and underinsured who were eligible to seek care in 1365 FQHC's that existed in the US and served more than 14 million people.(2007). The populations served by these centers bear a disproportionate cancer burden and had lower levels of screening for breast (58% vs. 70%), cervical (69% vs 82%), and colon cancer (20% vs 40%) compared to the general population.(2003,2004,2000) Work to close these gaps has been encouraged through collaboration between the NCI, Centers for Disease Control, Health Resources and Services Administration(HRSA) and FQHCs in the Cancer Collaborative (CC).The CC approach to planning cancer screening process in health centers has now

been proposed as a general process in HRSA's efforts to address health disparities.(2007) The work of the NCI with the VHA and HRSA's Health Disparities Collaboratives can serve as a foundation for developing technology that coordinates cancer care of people served by FQHCs.

The VA/NCI home centered coordinated cancer care system holds promise for the thousands of Veterans who have cancer and people who are at an earlier point in the cancer care continuum. We expect this current project to standardize and extend the model to others outside the VA, including those served by FQHCs.

NOTE: The National Cancer Institute (NCI) promotes the use of state-of-the-art media technology to develop tools, interventions, programs and systems that 1) are needed by professionals or the public to reduce cancer risk or improve the quality of life of cancer survivors; 2) help fill gaps in research; 3) resolve barriers to use so that products can be used effectively in medical and community settings; and 4) improve communication behaviors between primary care professionals and patients/care-givers in cancer-related matters.

Phase I activities and expected deliverables:

- Develop a system prototype that registers referrals, appointments, and all patient-provider and provider-provider communication throughout the coordination of the diagnostic process.
- The software prototype should include a real time visual simulation of the coordination process with alerts, reminders and other signals that support the patient's progress, the accountability of individual team members, and the integrity of the entire coordination effort.
- This program must be capable of integrating into a larger system of home based coordinated cancer care; avoid redundant documentation.
- Review the VA/NCI cancer care coordination model, other coordination protocols and relevant literature to develop an overall cancer coordination process model.
- Establish a team or set of teams that includes providers in FQHCs who will conduct cancer care coordination during the diagnostic process.
- Conduct interviews with team members and selected community participants to develop a set of use case scenarios (from first abnormality (abnormal screening test or symptomatic presentation in a physician's office through diagnosis for one cancer type) that will serve as the basis of the coordination simulation software program.
- Convene focus groups or conduct interviews with potential end-users of the system to determine if the system contents, format, etc. are appropriate for ease of use.
- Provide a report detailing the coordination tracking program design, including theoretical and methodological bases for the evaluation.
- Provide a set of use case scenarios that have been approved by members of the team for tracking.
- Develop a working prototype of the cancer care coordination tracking program.
- Include in the proposal, letters of agreement from organizations participating in Phase I feasibility testing and evaluation.
- Obtain letters of agreements from appropriate community participants to participate in the testing and evaluation of the final product in the Phase II.
- Present Phase I findings and demonstrate the final prototype to an NCI Evaluation Panel.

NOTE: Offerors are required to fully develop their individual product in Phase II to meet the goals of this SBIR contract topic. Where feasible and appropriate, Phase II contractors may be required to collaborate, coordinate, or communicate with other NCI funded contractors or programs. Offerors are also required to develop a dissemination package that enhances marketability.

Phase II activities and expected deliverables:

- Complete 2 iterations of the tracking program software, including technical documentation of the system and a training manual.
- Develop evaluation measures.
- Evaluate and refine the program based upon user feedback.
- Integrate the tracking program into a telehealth monitoring and computerized patient record.
- Test and evaluate the complete system serving cancer patients and their care coordination team using process and outcome measures as described above.
- System Requirements include:
  - Embedding the tracking software into a home telehealth monitoring and reporting system based upon the VA/NCI model of home centered coordinated cancer care; this could involve partnering or licensing with other vendors or developers of these components.
  - Integrating the home centered coordinated cancer care system into a community's existing IT infrastructure using the IT interoperability standards offered by The U.S. Department of Health and Human Services (www.hhs.gov/healthit). Eligible communities are those that have been funded by The Foundation for eHealth Initiative which provides seed funding and support to multi-stakeholder collaboratives within communities (both geographic and non-geographic) who are using electronic health information exchanges (HIE) and other information technology tools to drive improvements in healthcare quality, safety, and efficiency (www.ehealthinitiative.org).
  - Evaluating the system in a real community setting, according to cost, quality of care, quality of life and access outcome measures in addition to the community's own health and IT standards. Community members should be included in the research and development team from the beginning of the research and development project.
- In the first year of the contract, provide the program and contract officers with a letter of commercial interest.
- In the second year of the contract, provide the program and contract officers with a letter of commercial commitment.
- Include $24,000 in the budget for evaluation of the product at NCI's Evaluation Lab.
- Present final research findings and demonstrate the final product at an NCI/DCCPS sponsored Product Showcase.
- Prepare at least one manuscript describing the development and evaluation of the system for publication in a peer-reviewed scientific journal.
- Submit final report in the template provided by the NCI program officer.

249 System to Analyze and Support Biomarker Research and Development Strategies

Number of anticipated awards: 3-4

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $750,000

Because of the rapid expansion of the worldwide biomarker research data in volume and breadth, there is a critical need for integrating all of these data within a knowledge management system that supports automated review and evaluation of current research and development efforts, particularly within the context of all cancer research and therapeutic and diagnostic product development. Such a system permits rapid identification and decision-making to allocate resources where they can most efficiently be used to enhance product development.

Thus, the objective of this project is to expand the present methodology of biomarker research data analysis and strategic planning using a system that allows review and analysis of biomarker research and development projects as they relate to available worldwide data. The system would permit rapid identification and correlations of parameters of interest to the users' senior scientific staff, while

simultaneously providing high-efficiency development pathways for program areas of interest. The system should incorporate parameters allowing evaluation of methods/assays, tissue and disease specificities, clinical applications, and regulatory and clinical development status. The system when fully developed may be applied over a broad range of technologies such as genomics and proteomics, imaging modalities, immunohistochemistry, and histopathology. Also, when fully developed, the system should be usable by the private sector (e.g., pharma, biotech, diagnostics industries, etc.) and the public sector (e.g., NCI programs such as Developmental Therapeutics, SPOREs, EDRN, Cancer Imaging, OBQI, PACCT, NTROI, and intramural and extramural investigator-initiated research). Potential offerors can propose projects to comprehensively include all relevant cancer-related biomarkers or specific subsets (e.g., toxicity biomarkers) under a relational database system.

An example application would be selection of a biomarker of a molecular target (e.g., a mutated tyrosine kinase), all published drugs/chemicals that interact with the target, all cancer target organs that have the biomarker and in what incidence, stage(s) of cancer progression where the biomarker is found, existing assays to measure the biomarker and their states of development and use, toxicity associated with biomarker modulation, etc.

Project goals:

The core of the system will be a database cataloging and classifying the biomarker research projects with links to the original data sources. The remainder of the system will be tools (reports and algorithms) for summarizing, analyzing, and integrating the data with other sources. Multiple parameters describing the biomarkers cited shall be extracted into the database—e.g., biomarker name, clinical use, cancer target organ (clinical and non-clinical), specimen source, technology/assay methodology and/or assay target, biological process related to neoplastic progression (e.g., angiogenesis, proliferation, apoptosis), signaling pathway, drug or other intervention used in study (as appropriate), biomarker category (e.g., prognostic, predictive, risk, drug effect), disease stage, study population demographics, and phase of clinical study. The database shall be fully searchable (for individual records and categories of data) on all these parameters. The database shall be capable of supporting a large base of concurrent users via a user friendly, web-based user interface.

The database and other components of the system shall be built with open source code compatible with current industry and NCICB standards (e.g., J2EE, ANSI compliant SQL and Eclipse). Since NCI has invested substantially in developing informatics for cancer-specific uses, where possible, applications previously developed by NCICB should be leveraged. For example, applications developed for the Cancer Bioinformatics Grid (caBIG) should be considered, and the system should be integrated with caBIG applications, if appropriate. The system should be fully integrated with the NCI Enterprise Vocabulary System (EVS) and should use EVS terminology (and should comply with NCI's Cancer Data Standards Repository (caDSR) metadata standards, using NCI approved Common Data Elements where appropriate). However, the system developed should be compatible with other users' specific requirements.

System and user documentation shall be provided, quality control procedures shall be developed and applied to maintenance of the system, and quality assurance audits shall be carried out periodically. The project shall also include organization and administration of technical and scientific advisory groups involved in the design and implementation of the system.

Phase I activities and expected deliverables:

- Review a large, representative sample of relevant biomarker data and literature to develop an overall biomarker research program analysis and support model. Determine what, if any, algorithms exist to convert present research portfolio databases (electronic, manual, and hybrid) into an integrated automated knowledge management system that fulfills strategic research and business planning requirements for multiple users.
- Determine what, if any commercial software products exist that may serve as a platform for the proposed research program analysis and support tool. For example, the proposed product might be best developed as an add-on to an existing portfolio management package.
- Convene a focus group of senior scientists to solicit input on the scientific content and functionality required for the proposed product.

- Evaluate the availability of research data in the world-wide scientific literature with respect to the desired selection and measurement parameters. Identify problems with comparability and availability of research and administrative data over time and as collected by different systems.

- Develop a statement of functional requirements and user interface requirements for the product.

- Develop a prototype of the system using a representative sample of biomarkers.

- Include funds to present Phase I findings and system design.

Phase II activities and expected deliverables:

- Conduct a formal usability study of the software with representative users to evaluate the prototype system developed in Phase I. Enhance and modify the prototype's functionality and user interface based on this feedback.

- Complete two iterations of the tracking program software, including technical documentation of the system and a training manual. Documentation of the system design, business procedures (SOPs), data sources, data extraction guidelines and evaluation criteria shall be prepared. An indexed/searchable User Guide describing data sources, data parameters, evaluation criteria, and system functionality (e.g., searching, report generation and linking to data sources) shall be prepared. SOPs shall include quality control procedures for data entry (e.g., data edit checks).

- Develop and implement a project plan for populating, updating, and maintaining the biomarkers database.

- Develop evaluation measures.

- Demonstrate the flexibility of design that would permit updating the software as new biomarkers, research modalities, treatments, data formats, or other parameters of interest are added.

- Documentation of the database design, business procedures (SOPs), data sources, data extraction guidelines and evaluation criteria shall be prepared upon implementation of the database and shall be updated annually. An indexed/searchable User Guide describing data sources, data parameters, evaluation criteria, and database functionality (e.g., searching, report generation and linking to data sources) shall be prepared and loaded on the database website. SOPs shall include quality control procedures for data entry (e.g., data edit checks).

- Identify Phase II barriers to evaluating the impact of the software and resolutions to these barriers.

- In the first six months of the first year of the contract, provide the program and contract officers with a letter of commercial interest to either purchase or subscribe to the system once it is created.

- In the first six months of the second year of the contract, provide the program and contract officers with a letter of commercial commitment based on the successful outcome of the Phase II. It is anticipated that potential customers would be the NCI, NIH, and others in the public sector; and pharma, biotech, diagnostics industry, clinical laboratory industry, and others in the private sector.

250 Biopsy Instruments and Devices that Preserve Molecular Profiles in Tumors

Number of anticipated awards: 4

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: $250,000; Phase II: $2,000,000

Project duration: Phase I: 6-12 months; Phase II: 2 years

Molecular medicine holds much promise for advancing cancer diagnosis and treatment, if biomarkers, molecular targets and drug effects on these targets can be accurately assessed in tumor nodules in the viscera. The amount and function of molecular drug targets within signal transduction pathways are often regulated by rapid enzymatic reactions in response to physiological stimuli.

Biopsies play a central role in assessing biomarkers and molecular targets in solid tumors, but conventional practices and medications used by surgeons and interventional radiologists necessarily perturb the tumor environment and thereby induce extraneous and confounding molecular responses to tissue trauma, vascular changes, hypoxia, anesthetics, etc. Expeditious processing of the biopsy specimen using snap freezing or rapid fixation are ineffective for preventing many rapid enzymatic modifications, because time frames of biopsy procedures are much longer than that of the enzymatic reactions. Thus, there is a need to develop clinical devices, instruments and approaches suitable for clinical practice that stabilize molecular profiles in visceral tumor lesions during the procedure, and prevent molecular response to the procedure. The diagnostics market includes devices for needle cryobiopsy of breast lesions that freeze the tissue in situ before sampling, but the needle size is too large for percutaneous image-guided biopsy of visceral sites. Although unlikely to improve routine diagnostic biopsies, innovative approaches for tumor biopsy that preserve the molecular profile will create an entirely new diagnostic area and market in molecular therapeutics, which will not only facilitate pharmacodynamic assessment of targeted therapeutics but also enable individualized molecular therapy of solid tumors based on accurate information about signal transduction pathways, molecular drug targets and biomarkers.

Project goals:

The short-term goal of the project is the identification of technical strategies with potential for stabilizing the molecular profile of cancerous lesions in visceral tissue sites during clinical biopsy procedures. The long-term goals of the project are the design and development of operational prototype instruments/devices required to practice the innovative biopsy approach; the demonstration of the operational success of the innovative approach when applied to visceral lesions of solid tumors in model systems; and the evaluation of the potential superiority of the innovative biopsy approach over conventional surgical and radiological procedures for assessing highly dynamic molecular profiles that are associated with a high degree of instability during conventional biopsy procedures. The project scope includes advancements in biopsy technologies and approaches from any medical discipline performing biopsy procedures (surgery, radiology, dermatology, etc.) that improve the fidelity of molecular assessment of visceral tumor lesions. Reaching these goals on the basis of experimental evidence will mark a major advance in the ability to accurately assess the molecular profile of solid tumor lesions of the viscera and the functional status of their molecular targets during early clinical trials of experimental therapeutics. If successful, this project will improve the accuracy of biomarker assessment for diagnosis and prognosis and the information available about the pharmacodynamics and molecular efficacy of targeted drug therapy.

Phase I activities and expected deliverables:

- Identify a technical strategy for preventing changes in molecular status during solid tumor biopsy and articulate its rationale and critical principles of operation.
- Demonstrate the feasibility of achieving the critical principles of the innovative biopsy procedure during biopsy of solid tumor lesions in visceral tissue.
- Demonstrate that the innovative biopsy procedure stabilizes a biochemical process or reaction, or a functional molecular status, that is unstable during conventional surgical or needle biopsy procedures.
- Provide a description of the technical strategy underlying the innovative biopsy approach, the critical operating principles and the experimental design for testing if feasibility has been achieved.
- Provide a summary report of the results proving the feasibility of the innovative biopsy approach in tumor lesions of the viscera.
- Produce histochemical, biomarker, and/or other pharmacodynamic data that demonstrate that the innovative biopsy approach stabilizes a biochemical or molecular endpoint that is unstable during conventional biopsy procedures.

Phase II activities and expected deliverables:

- Design, build and test any innovative biopsy instrument/device required for the new biopsy procedure.
- Develop and validate necessary assays for assessing molecular preservation of at least three biochemical pathways/endpoints that will be useful

indicators of molecular stability or instability in solid tumor biopsies from visceral tissue, one of which is suitable to be a general quality control indicator of molecular stabilization in clinical specimens and another of which is a molecular drug target.

- After obtaining appropriate IACUC approval, design and conduct comparative studies of the innovative biopsy approach, conventional surgical biopsy and conventional needle biopsy of visceral lesions of a solid tumor model in animals, using validated assays for at least three biochemical pathways/endpoints , including the quality control indicator and the molecular drug target.

- After obtaining appropriate regulatory approval, design, conduct and use the validated assay(s) in a proof-of-concept clinical trial in solid tumor patients that will test if the innovative biopsy approach is capable of stabilizing at least the quality control indicator of molecular stabilization in biopsies of visceral disease.

- Produce a prototype device or instrument that can be used to obtain molecularly preserved biopsies of solid tumors in visceral organs of large animal models such as canine models.

- Provide written instructions for the operation of any prototype biopsy device or instrument and the procedure for performing the innovative biopsy with quality control measures.

- Provide data confirming that the prototype device/instrument operates within design and performance specifications when used in the veterinary environment.

- Provide results of the comparative study of the innovative and conventional biopsy approaches in the animal model, using the developed and validated assays of at least the three biochemical pathways/endpoints above, one of which must be the quality control indicator and another of which must be a molecular drug target.

- Provide results of the proof-of-concept clinical trial of the innovative biopsy approach applied to visceral solid tumor lesions, including the safety of the innovative procedure, the reliability of the device, and the assay results at least for the quality control indicator of molecular stabilization.

251 Development of Anticancer Agents

Number of anticipated awards: 7

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $1,500,000

The short term goal of this SBIR contract topic is to create a mechanism whereby candidate therapeutic agents of interest to NCI can be further developed by small businesses. (For a list of the compounds of interest to NCI, please see: http://sbir.cancer.gov/.) (If required, commercialization licenses must be separately negotiated with NIH's Office of Technology Transfer (OTT) and could take the form of a Commercial Evaluation License, a Non-Exclusive License or an Exclusive License to perform pre-clinical development.) Work scope may include animal efficacy testing, SAR, medicinal chemistry, formulation, production of GMP bulk drug and clinical product, pharmacokinetic, pharmacodynamic, and toxicological studies. These data will establish the rationale for continued development of the experimental therapeutic agent to the point of filing an IND. Ownership of all intellectual property generated in these experiments will be determined by patent law although it is anticipated that experimental data generated by the small business will be owned by the small business, and it may use this information to continue developing the agent independently, or partner with academia or industry in bringing this agent to the clinic (if required, Non-exclusive or Exclusive Licenses must be separately negotiated with the OTT). Successful projects will also be eligible for further development at NCI, including early-stage clinical trials via the Joint DCTD-CCR Early Therapeutic Development Program. Non-confidential summaries of compounds available for development will be available on the following web site. Potential applicants will submit a letter of intent and sign a confidentiality agreement in order to receive confidential data on these compounds. For more information, please go to (http://sbir.cancer.gov/).

Companies may also submit proposals for the development of their own agents that are in mid to

late pre-clinical development. The development plan, targeted to oncologic indications, will be reviewed by NCI. Overall priority will be given to proposals to develop NCI compounds.

Project goals:

The goal of the NCI SBIR program is to fund small businesses to develop commercially viable products that advance the research and development needs of the Institute. The NCI Strategic Plan identifies integrating clinical trial structures to expedite identification of the most promising treatment opportunities and rapid execution of the necessary clinical trials as a strategic priority (Strategy 4.5). Part of this strategy includes creating an integrated infrastructure to accelerate the implementation of high-priority clinical trials. The long term goal of this contract is to enable a small business to bring a fully developed cancer therapeutic agent to the clinic and eventually to the market.

The NCI's new joint DCTD-CCR initiative for oncology therapeutics development (The Joint DCTD-CCR Early Therapeutic Development Program) seeks to address this strategic objective by reviewing a broad range of candidate therapeutic agents of interest to NCI's basic and clinical investigators, with the goal of capitalizing on FDA's Exploratory IND Guidance to initiate clinical testing at the earliest feasible point in a compound's development.

TRACK I would focus on the development of compounds identified by NCI. The agents being made available by NCI under this solicitation will be in mid to late preclinical development stages (expected time to clinic 1-3 years). NCI has an expressed interest in further development of these agents. Awardees will benefit in several ways:

- Recommended IND-directed development plan will be prepared by NCI. The offeror is free to propose any procedures or innovative approaches that can shorten the drug development timeline.
- NCI IP available for licensing – small businesses will be able to capitalize on the investment that NCI has already put into these compounds.
- Potential for an early-stage clinical development partnership with NCI upon project completion.

Phase I activities and expected deliverables:

- Specific activities will range from SAR and medicinal chemistry to animal toxicology and pharmacology, depending on the agent selected for development. The available agents are listed at: (http://sbir.cancer.gov/).
- Mutually agreed-upon development plan that describes in detail the experiments necessary to file an IND or an exploratory IND.
- Demonstrate ability to deliver results for the initial set of experiments (project-specific, according to the development plan above).

Phase II activities and expected deliverables:

- Complete all experiments according to the development plan (can be re-evaluated if needed).
- If warranted, provide sufficient data to NCI to file an IND or an exploratory IND for the candidate therapeutic agent in question (oncologic indications).
- Demonstrate the ability to produce a sufficient amount of clinical grade materials suitable for an early clinical trial (according to FDA's Exploratory IND guidance). http://www.fda.gov/cder/guidance/7086fnl.htm
- A comprehensive IP and development plan, outlining how the small business will develop and commercialize the subject therapeutic agent. If relevant, finalize clinical co-development agreement with NCI.

TRACK II would allow the development of compounds identified from within the company. The agents should be in mid- to late-stage preclinical development (expected time to clinic 1-3 years). Overall priority will be given to proposals to develop NCI compounds. However, TRACK II awardees will also benefit in several ways:

- If appropriate, NCI will provide assistance to the small business in its development of an IND-directed development plan. Assistance might include assistance in study design and identification of

necessary studies that would be appropriate for filing of an IND.

- Potential for further collaboration with NCI inventors/investigators.
- Potential for an early-stage clinical development partnership with NCI upon project completion.

Phase I activities and expected deliverables:

- Specific activities will range from SAR and medicinal chemistry to animal toxicology and pharmacology, depending on the agent selected for development.
- Mutually agreed-upon development plan that describes in detail the experiments necessary to file an IND or an exploratory IND.
- Demonstrate ability to deliver results for the initial set of experiments (project-specific, according to the development plan above).

Phase II activities and expected deliverables:

- Complete all experiments according to the development plan (can be re-evaluated if needed).
- If warranted, provide sufficient data to file an IND or an exploratory IND for the candidate therapeutic agent in question (oncologic indications).
- Demonstrate the ability to produce a sufficient amount of clinical grade materials suitable for an early clinical trial (according to FDA's Exploratory IND guidance). http://www.fda.gov/cder/guidance/7086fnl.htm
- A comprehensive IP and development plan, outlining how the small business will develop and commercialize the subject therapeutic agent. If relevant, finalize clinical co-development agreement with NCI.

252 Nanotechnology Imaging and Sensing Platforms for Improved Diagnosis of Cancer

Number of anticipated awards: 3-5

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $1,000,000

Nanotechnology involves the design, synthesis, and manipulation of materials at the nanoscale to take advantage of novel material properties (e.g., large surface to volume ratio, increased conductivity, enhanced imaging contrast, etc.) that are not normally present in conventional bulk length scales. These properties render nanomaterials ideal candidates for imaging, sensing, and detecting purposes. Further functionalization can be achieved by conjugating biological ligands (e.g., oligonucleotides, short peptide sequences, antibodies, etc.) that can serve to achieve specific targeting of cells/tissues/organs or specific capturing of genomic/proteomic candidate biomarkers.

For several types of cancer, the primary cause of poor survival is late detection, most often after the disease has spread to distant sites. For example, most melanomas that are found without evidence of metastasis can be cured with surgical resection. In contrast, for patients with advanced or metastatic melanoma, the prognosis is poor (a 5-year survival of 5-10%). Consequently, efforts are currently being made to develop new diagnostic solutions comprising imaging and/or monitoring of prognostic biomarkers.

To accelerate such efforts, the National Cancer Institute (NCI) requests proposals for the development of commercially-viable nanotechnology-based imaging agents and/or sensing platforms that will ultimately assist and improve current clinical protocols of cancer detection and diagnosis.

Project goals:

The goal of the project is to develop nano-enabled platforms that can provide increased resolution both spatially, and more importantly, temporally, in detecting cancer that would ultimately offer clinicians a way to maximize the chance of positive clinical prognosis. The platforms can be used for early detection/imaging of initial onset of disease, or be used as post-treatment monitoring to detect/image recurrence of disease. Strategies can also include screening assays that provide a better mechanistic understanding of metastasis which can help develop better therapies and further improve patient outcome. As current drug development continues to rely mainly on reductions in overall size of tumors,

many validated compounds may not work on metastatic disease. Novel imaging and sensing diagnostic nanoplatforms could also be used, in a preclinical setting, both for high-throughput screening assays to locate new metastasis-directed compounds and for validating the new compounds in vitro, in situ, and ultimately, in vivo.

Potential relevant imaging and sensing nanoplatforms could include, but are not limited to:

Imaging and Sensing Nanoparticles

- Examples: Fluorescent agents (e.g., quantum dots, quantum rods); medical imaging agents (e.g., MR, CT, SPECT, PET); in vivo sensors (e.g., FRET sensors, biologically-activated systems).
- Potential Applications: Use of agents as secondary-tags to improve existing in vitro/ex vivo assays; Detecting smaller lesions and/or better delineation of tumor margins with traditional clinical imaging modalities (e.g., MR, CT, PET) before, during, and after interventions (e.g., resection, chemotherapy); Novel in vivo sensors to monitor cancer biology-related activities (e.g., enzymes, cleaved peptides).

Nano-enabled Sensing Platforms

- Examples: Use of functionalized nanomaterials (e.g., nanowires, nanotubes, nano-cantilevers) to build sensing platforms with optical or electrical output.
- Potential Applications: Novel platforms that would enhance sensitivity/specificity of existing candidate biomarker detection and validation; Sensing of tumor metastasis and/or recurrence post-treatment.

High-throughput Screening Nanoplatforms

- Examples: Single or combinations of nanotechnologies (e.g., nanopatterning, imaging agent, sensing platform, microfluidics) for assay development.
- Applications: Locating novel cancer biomarkers that may be undetectable using traditional assays; detecting cellular changes using nano-sensors to screen for novel therapeutic agents.

Given the diversity of potential applications discussed above, submitted proposals should place emphasis on the specific nanotechnology-enabling component of the proposed platform.

Phase I activities and expected deliverables:

- Design describing:
  - Sensing/imaging methodology
  - Unique spatial/temporal capabilities enabled by nanotechnology
  - Proof of concept experiments
  - Benchmarking experiments against conventional methodologies
- First-stage validation of design in relevant preclinical samples as listed below,
  - Medical imaging agents: In vivo small animal efficacy studies
  - Sensing platforms: Candidate biomarkers in serum-free samples
  - High-throughput imaging and screening assays: Non-primary cell lines and/or tissue samples
- Successful completion of benchmarking experiments demonstrating a minimum of 2x improvement against conventional methodologies.

Phase II activities and expected deliverables:

- Second-stage validation of design for potential clinical adaptation:
  - Medical imaging agents: In vivo small animal toxicology studies that can be used for regulatory filing purposes
  - Sensing platforms: Candidate biomarkers in patient samples
  - High-throughput imaging and screening assays: primary cells and/or tissues obtained from patients
- Submitted IDE application to obtain necessary regulatory approval for clinical validation.

253 Advances in Protein Expression of Post-Translationally Modified Cancer Related Proteins

Number of anticipated awards: 4

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $1,000,000

Release of a completed polypeptide chain from a ribosome is often not the last chemical step in the formation of a protein. Various covalent modifications often occur, either during or after assembly of the polypeptide chain. Most proteins undergo co- and/or post-translational modifications. Knowledge of these modifications is extremely important because they may alter physical and chemical properties, folding, conformation distribution, stability, activity, and consequently, function of the proteins. Moreover, the modification itself can act as an added functional group. Examples of the biological effects of protein modifications include phosphorylation for signal transduction, ubiquitination for proteolysis, attachment of fatty acids for membrane anchoring and association, glycosylation for protein half-life, targeting, cell:cell and cell:matrix interactions. Consequently, the analysis of proteins and their post-translational modifications (PTMs) is particularly important for the study of heart disease, cancer, neurodegenerative diseases and diabetes.

Therefore, the NCI is interested in proposals that focus on the development of post-translationally modified human proteins (e.g., glycosylation, phosphorylation, acetylation, oxidation). Proposals should explicitly describe how the proposed technology/system will develop/express, isolate and characterize the PTMs.

Project goals:

Increasing demand for recombinant PTM proteins has focused research on techniques for improving protein expression and controlling post-translational processing. The purpose of this project is to stimulate the development on all aspects of PTM protein expression including chemical synthesis, novel cell systems, expression vectors, and culture conditions. Proteins selected for production are to entail low abundance cancer related proteins from bodily fluids in support of the Clinical Proteomic Technologies Initiative (http://proteomics.cancer.gov). These proteins are to become part of CPTI's Reagents and Resource core.

Phase I activities and expected deliverables:

- Demonstration of feasibility of the innovative PTM development approach.
- Generate at least 10 PTM targets. Offerors must select from the following list of the NCI required targets listed at: http://sbir.cancer.gov/
- Produce an initial PTM production prototype in working with the Clinical Proteomic Technologies Initiative community.
- Produce evidence that the PTMs are well characterized (preferably using MS-based techniques).
- Demonstrate that PTMs can be made reproducibly and economically.
- Research should be proposed with quantitative feasibility milestones.

Phase II activities and expected deliverables:

- Generate at least 100 PTM targets (targets to be selected in coordination with the Clinical Proteomic Technologies Initiative community).
- PTMs are to be well characterized (preferably using MS-based techniques).
- Project to be done in coordination with the Clinical Proteomic Technology Initiative community to integrate PTMs into the technology assessment programs and greater scientific community.
- Research should be proposed with quantitative feasibility milestones.

254 Development of Clinical Quantitative Multiplex High-Throughput Mass Spectrometric Immunoassay for Detecting Low Abundance Cancer Related Proteins/Peptides in Bodily Fluids

Number of anticipated awards: 4

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: $150,000; Phase II: $1,000,000

The application of proteomics tools in the clinical setting lags far behind their use in basic science and drug discovery. In the past, protein/peptide

biomarkers were tested individually to determine their value using common techniques such as ELISA, 2-D gels, and mass spectrometry. Each of these technologies has its advantages, but they still suffer from an inability to quantitatively evaluate multiple markers in a single reaction. However, recent applications of affinity mass spectrometry into clinical laboratories brought a renewed interest in mass spectrometric immunoassays as a more specific affinity method capable of selectively targeting and studying protein biomarkers. In mass spectrometry-based immunoassays, proteins are affinity retrieved from biological samples via surface-immobilized antibodies, and are then detected via mass spectrometric analysis. The assays benefit from dual specificity, which is brought about by the affinity of the antibody and the protein mass readout. The mass spectrometric aspect of the assays enables single-step detection of protein isoforms and their individual quantification.

Therefore, the NCI is interested in proposals that focus on developing a multiplexed mass spectrometric immunoassay for the detection of low abundance cancer related proteins/peptides from bodily fluids (examples of "bodily fluids" include plasma or serum, serous fluids collected from ductal lavage, but not cell lysates or tissue culture media). Proposals should describe how the proposed technology will be highly specific, highly selective and have ultra-sensitive detection capabilities (at least within the ng/mL range) with limited sample preparation. Proposals should also distinguish any new methods of multiplex fabrication, novel immunoaffinity capture systems, and/or new detection/quantification systems. All responses must deliver a reasonable method for working with complex bodily fluids. In addition, maximum level of multiplexing, volume of sample requirement, with sample processing/analysis time must be addressed. Surface enhanced laser desorption ionization (SELDI) MS will not be considered for this SBIR due to its limited ability to comprehensively measure and identify low abundance proteins in serum or plasma considered to be within the dynamic range of proteins released from cancer cells.

Project goals:

Of the hundreds of thousands of proteins believed to be found in different body fluids, it is likely that cancer-related proteins will be in relatively low abundance. The development of effective technologies to accurately measure these proteins and improve our diagnostic capabilities by discerning diseased from non-diseased states requires the development of next-generation proteomic technologies. The purpose of this project is to stimulate the development of multiplexed mass spectrometric immunoassays for the detection of low abundance cancer related proteins/peptides from bodily fluids in support of the Clinical Proteomic Technologies Initiative (http://proteomics.cancer.gov). In addition, this tool as conceived is to be applicable in Cancer Centers and other settings where NCI Investigators conduct clinical care.

Phase I activities and expected deliverables:

During the Phase I proof-of-concept stage, offerors are encouraged (but not required) to pursue any of the biomarkers listed in the following reference: Malu Polanski and N. Leigh Anderson. (2006) "A List of Candidate Cancer Biomarkers for Targeted Proteomics." Biomarker Insights 2:1-48

- Demonstration of feasibility of the innovative approach.
- Produce an initial product prototype in working with the Clinical Proteomic Technologies Initiative community.
- Conduct usability testing with product prototype with representative users (e.g., Clinical Proteomic Technologies Initiative community).
- Make modifications to the prototype based on results obtained from usability testing.
- Compare findings to ELISA-based technologies. Detection limits should aim to be measured and reported as absolute quantitations that equal or surpass current ELISA measurements.
- Prototype requirements include sample volumes less than 50 microliters, multiplex a minimum of 5 markers, high sensitivity (detection limit lower than 5 picogram/microliter), high reproducibility (CV's less than 10%), and broad dynamic range (gram/Liter to nanogram/Liter).
- Establish prototype revisions/additions to be implemented and tested in Phase II.
- Present findings to an NCI Evaluation Panel.

- Research should be proposed with quantitative feasibility milestones.

Phase II activities and expected deliverables:

- Implement strategy and project plan for a fully functional quantitative, automated high-throughput multiplex affinity/protein capture technology for detecting low abundance cancer related proteins/peptides from bodily fluids.
- Specificity greater than 95%.
- Development of an affinity/protein capture technology with multiplexing capability up to 50 analytes (proteins/peptides) that implements the features, functions, and requirements developed in Phase I.
- Project to be done in coordination with the Clinical Proteomic Technologies Initiative community to integrate platform into the technology assessment programs and greater scientific community.
- Validate findings to ELISA.
- Research should be proposed with quantitative feasibility milestones.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

The NHLBI plans, conducts, fosters, and supports an integrated and coordinated program of basic research, clinical investigation, and trials, observational studies, and demonstration and education projects. The Institute's mission includes studies related to the causes, prevention, diagnosis, and treatment of heart, blood vessel, lung, blood, sleep disorders, and blood resources management. Studies are conducted in its own laboratories and by other scientific institutions and individuals supported by research grants and contracts. The NHLBI SBIR program fosters basic, applied, and clinical research on all product and service development related to the mission of the NHLBI.

This solicitation invites proposals in the following areas.

038 Production of Generic Modified Hemoglobin

(Fast-Track proposals will be accepted.)

The quest to bring hemoglobin-based oxygen carriers (HBOCs) to market began well over a half century ago. Recent clinical experiences in the U.S. with candidate HBOCs however have not resulted in the availability of licensed products primarily due to toxicities observed in a number of clinical trials. While the past decade has seen significant efforts from the commercial sector of product design and evaluation, a true understanding of the basic science underlying the observed toxicities and basic physiology of hemoglobin-based solutions is lacking. Fundamental research studies are clearly needed but it is extremely difficult if not impossible for some investigators to obtain sufficient quantities of these products to conduct research studies. This situation is due to a variety of reasons including limited availability of products or the proprietary nature of certain commercial products. For knowledge in this field to grow at a more rapid rate, there is a fundamental need for a source of HBOCs which would be available to support and accelerate research efforts in this area. The availability of such products will benefit those investigators who have had a long standing interest in addressing basic research questions as well as new investigators and investigators who may have never worked in this area but would do so if HBOCs were available.

The goal of this solicitation is the development and production of generic modified hemoglobin(s) for research purposes which would be made available to the scientific community interested in pursuing research studies in this area. The homogenous raw materials must be well defined in their physico-chemical characteristics (e.g., Hb/metHb, P50, MW profile, pH, electrolytes, stability, endotoxin test, viral inactivated, etc), produced under good manufacturing practices (GMP), be uniform from batch to batch, and certified by quality control. The products may range from solutions of native hemoglobin (A0), stroma free hemoglobin (SFH), to a variety of modified forms. The successful offeror must have a high quality production facility available, know protein molecular, biochemical and extraction techniques and have experience in biochemical modifications.

Phase I proposals should focus on the development of a well-characterized generic hemoglobin solution(s) for research purposes. Investigations in this phase shall involve laboratory bench and early scale-up studies.

Phase II proposals shall focus on scale-up and production of a HBOC(s) under GMP. Enough product(s) shall be produced to satisfy the research

needs of U.S. investigators interested in pursuing fundamental research studies on HBOC.

039 Aged Animal Resources for Cardiovascular Disease Research

(Fast-Track proposals will be accepted.)

The incidence of several major cardiovascular diseases increases dramatically in older Americans, yet basic science studies designed to elucidate disease mechanisms are most often conducted in relatively young animal models for short periods of time. There are very few longitudinal basic science studies in experimental animal models to examine how purported disease mechanisms may be influenced by the aging process. This fact is largely due to the lack of appropriate animal models of human cardiovascular disease and the expense of developing and maintaining aged animal resources. Such resources are few, and many of those that do exist, such as the National Institute of Aging Aged Rodent Colonies Resource, are only available to a select group of researchers, rather than the general scientific community. The goal of this solicitation is the development and production of an aged animal resource for elucidating the influence of the aging process on development and progression of cardiovascular diseases.

For instance, in the United States, the incidence of coronary heart disease increases from 15.5/1000 person years in African-American women aged 65-60 to 37.5/1000 person years in the same segment of the population aged 75-79. Similar increases in the incidence of coronary heart disease are observed over the same range of ages in African-American males and Caucasian men and women. Also, in the United States, 80% of atrial fibrillation occurs in patients over the age of 65 years, and its prevalence tracks that of heart failure. Of the nearly five million patients in the United States with heart failure, 75% are aged 65 and older. The incidence of congestive heart failure has been shown to increase 9% with each year of age over 65 and is greater than 6% per year in Caucasian men and women aged 85 and older. Thus there is an urgent need to develop appropriate models of cardiovascular disease and the effects of aging in aged animals.

Phase I proposals should focus on the choice of the most appropriate animal models for studying the effects of aging on cardiovascular disease development and progression as well as developing a facility to house and distribute aged animals for research purposes.

Phase II proposals should focus on scale-up and production of the resource and its continuation. Included in these efforts should be advertising of the existence of the resource and development of collaborations within the research community to assure long-term maintenance of the resource.

040 Nanoprobes for Non-Invasive Detection of Atherosclerotic Plaques

(Fast-Track proposals will be accepted.)

Coronary heart disease is a major cause of death and disability in the U.S. and other industrialized societies. The underlying cause, in most cases, is the development of atherosclerotic lesions in the coronary arteries. The atherosclerotic lesion progresses largely in a clinically silent and asymptomatic manner to form plaques that severely block the coronary arteries. Many of these plaques are prone to rupture resulting in acute coronary thrombosis and myocardial infarction.

Many of the factors involved in the atherosclerotic process have been identified and a complex interaction exists between the cellular entities involved in the atherosclerotic process. Endothelial cells, smooth muscle cells, platelets, leukocytes are all involved in the formation of an atherosclerotic lesion. Plaque erosion, stenosis, and hemorrhage are thought to be important in plaque rupture as are force imbalances within the plaque and acute changes in intraluminal coronary pressure. Currently, a significant limitation to early detection is the unavailability of non-invasive imaging modalities for the detection of a developing plaque or a plaque that is prone to rupture.

The goal of this proposal is to develop nanoprobes for non-invasive or minimally invasive visualization/detection of a developing atherosclerotic plaque and its characteristics. Early detection of atherosclerotic plaques would be extremely useful in risk assessment and appropriate targeting of preventive measures. Further, early detection and characterization of atherosclerotic plaques susceptible to rupture may decrease morbidity and mortality.

Phase I proposals should address initial development and feasibility testing of novel technologies for plaque detection and Phase II proposals should be focused on completing the development of the technology for incorporation into the clinic. The work is expected to include in vitro and in vivo studies to demonstrate effectiveness.

041 Cardiovascular, Lung, And Blood Computational Model Library

(Fast-Track proposals will be accepted.)

Simulations of cardiovascular and pulmonary solid and fluid mechanics using finite element and computation fluid mechanics software enhance studies of cardiovascular, lung, and blood disease progression and treatments. Currently, simulations using human cardiovascular and pulmonary anatomy and blood rheology require reconstructing, collecting, and/or manipulating anatomical and rheological data. Generation of such models can be time-consuming, is typically completed independently for each simulation, and has not been standardized.

The objective of this solicitation is to address this problem by developing and maintaining a library of useful and relevant computational models of the cardiovascular and pulmonary anatomy and related blood and tissue material properties. Such a library would be a valuable resource in simulating the mechanics of and fluid mechanics within cardiovascular and pulmonary systems. Such simulations would, in turn, help to better understand function in these systems and to develop and simulate interventions, such as those provided by surgical procedures and prosthetic devices.

In the Phase I proposal, a limited number of simple cardiovascular, pulmonary, and blood anatomic and rheological models will be developed and/or incorporated from existing models or libraries into an initial database. The Phase I work will demonstrate (1) the ability to generate the appropriate models from existing and newly collected data and (2) that the generated models can be used to simulate cardiovascular and pulmonary solid and fluid mechanics. To facilitate model development, anatomic components of the library should, if possible, be modular so that custom, specific models can be built from the separate components.

Phase II proposals will complete the development of the methods to generate the models and expand the library to include the range of anatomic components of the cardiovascular and pulmonary systems and rheological models of blood. The library will include cardiovascular and pulmonary anatomy and blood rheology models for both normal and disease states. Phase II proposals should also include parameters and results of appropriate representative simulations which can be used to validate work performed by users of the library, and a method for users to rate and provide feedback about each model.

042 Refinement and Standardization of a Parvovirus B19 Vaccine

(Fast-Track proposals are accepted.)

The NHLBI has a long-standing interest in parvovirus B19, an important pathogen affecting humans. Parvovirus B19 infection is common among children and adults and is often asymptomatic. The infection can result in serious hematological conditions in susceptible children, particularly in sickle cell disease patients, who may develop life threatening transient aplastic crisis.

In the late 1980s NHLBI intramural scientists developed a candidate parvovirus B19 vaccine using recombinant DNA technology. In order to manufacture the vaccine in large quantities for Phase II/III clinical trials, several areas for process improvement must be addressed. The process refinement will focus on two areas of the Parvovirus B19 vaccine production:

- Pre-manufacture phase in which the contractor will develop a new master and working Sf9 cell stock; prepare master and working stocks of the two baculovirus (vp1 and vp2) used to manufacture the vaccine; improve control over the vp1 to vp2 ratio in the final product (vpl) and; determine time of harvest based on cell viability & maximum virus yield.

- Manufacture phase during which the contractor will scale up the vpl purification process; characterize acceptable range of yield and purity; finalize test procedures to quantify concentration of vpl in the final product and; optimize the vaccine formulation.

Therefore, the purpose of this solicitation is to establish well-defined procedures to improve and upgrade the production process of the parvovirus B19 vaccine currently undergoing a Phase I clinical. The anticipated process improvements would lead to the production of standardized clinical materials for Phase II/III clinical trials involving seronegative young adults and children with sickle cell anemia.

Phase I proposals should address the pre-manufacture steps identified above. In addition, description of measures to maintain strict adherence to current FDA requirements will be mandatory.

Phase II proposals should focus on the vaccine production stages process, addressing the topics mentioned above.

043 Development of Pathogen Inactivation Technologies for Blood Components

(Fast-Track proposals will be accepted.)

Great strides have been made over the past 25 years greatly improving the safety of the nation's blood supply. Current blood donor screening and laboratory testing has drastically reduced the risks of acquiring infectious disease through blood transfusion. However, the potential for new, emerging infectious agents entering the blood supply continues to be a serious concern of the blood banking community. Pathogen inactivation of blood and blood components provides an additional layer of protection from such agents. The effectiveness of pathogen inactivation technology is best exemplified with the virtual elimination of certain infectious agents from manufactured plasma derivatives. Since 1985, there have been no transmissions of human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) by U.S. licensed plasma derivatives. However, because of the labile nature of red blood cells and platelets, these technologies are far too harsh for use with cellular blood components. During the past several years, new technologies have been developed and evaluated in clinical studies offering hope that blood components can also be treated to destroy the infectivity of a wide array of microbial agents without significantly reducing the component's therapeutic effectiveness. These technologies include leukoreduction of blood, photochemical treatment of platelets or plasma with ultraviolet light and psoralen compounds, and various chemical treatments of red blood cells which may or may not involve irradiation with ultraviolet or visible light. Some of these technologies have been shown to reduce infectivity in a wide array of infectious agents. While much progress has occurred in the development of these technologies in recent years, there is still no U.S. licensed pathogen inactivation process for cellular blood components. There is a need to evaluate other new, promising compounds and procedures. It does not appear that any one inactivation technology will be effective in treating all classes of agents (e.g., viruses, bacteria, protozoa, prions). It is likely that a combination of techniques that remove and/or inactivate agents will be needed. These technologies are generally sophisticated and costly. They probably will be utilized by the developed world if found to be safe and effective. However, because of costs they will be out of reach for resource-poor countries where blood-borne agents are highly prevalent and laboratory screening irregular or nonexistent. In such settings, the availability of simple, cost-effective inactivation procedures could save millions of lives. This solicitation encourages research leading to the development of pathogen inactivation procedures for blood components, particularly red blood cells and platelets, although work on plasma components would also be responsive to this solicitation. Research on the development of simple, low cost procedures for use by less practiced laboratory personnel in the developing world would also be responsive and is highly encouraged.

The Phase I proposal shall focus on studies that provide proof of concept that the pathogen inactivation procedure is capable of reducing the infectivity of infectious agents in the blood component(s) while maintaining the function of the component at an acceptable therapeutic level. The inactivation kinetics of the infectious agents being studied shall be determined. The effect of the procedure on the viability of the blood component shall be determined using a variety of different approaches depending on the component such as flow cytometry studies to determine the extent of platelet activation, platelet aggregation studies or assays for the red cell storage lesion (e.g., extracellular potassium leakage).

Phase II studies will extend the efforts of the Phase I studies and shall focus on in vitro and in vivo studies and scale-up of the process and prototype device including ancillary equipment such as blood bags. Studies shall include the use of human blood in quantities comparable to those amounts to be treated in the blood bank. In vivo studies shall be designed to demonstrate acceptable product performance as predetermined by FDA regulations (RBC) or by agreement with FDA staff (platelets). The array of infectious agents to be tested can be expanded in this phase. The therapeutic effectiveness of the component shall be investigated. Safety studies of the treated component shall be conducted and shall include toxicity, reproductive toxicity, and mutagenic and carcinogenic potential.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM (NIAAA)

The NIAAA supports research on the causes, prevention, control, and treatment of the major

health problems of alcohol abuse, alcoholism, and alcohol-related problems. Through its extramural research programs, the NIAAA funds a wide range of basic and applied research to develop new and/or improved technologies and approaches for increasing the effectiveness of diagnosis, treatment, and prevention. The NIAAA also is concerned with strengthening research dissemination, scientific communications, public education, and data collection activities in the areas of its research programs.

This solicitation invites proposals in the following area:

030 Alcohol Biosensors and Data Analysis Systems

(Fast-Track proposals will be accepted.)

It is anticipated that innovative and improved alcohol biosensors would be useful in a variety of situations including, but not limited to: clinical monitoring, forensics and human or animal research. Specific sensor characteristics would complement their intended use. This applies to characteristics such as: sampling frequency, degree of accuracy, data storage capacity and data transmission frequency.

Also depending on their intended purpose and use, alcohol sensors may be augmented with additional information such as other physiological measurements or geospatial determinations.

For animals, the devices must be biocompatible and not interfere with behavior. For humans devices must additionally to be compatible with comfort, even when worn for weeks or months. Since alcohol readings are likely to be baseline most of the time, sensing devices generally require ways to monitor contact and readiness to record. Moreover, where necessary, measurement fidelity should be robust to subjects' activities including active efforts at tampering.

The mode of data storage will need to conform to power limitations and strategies for data transmission which may require telemetry.

In addition to alcohol monitoring and data transmission this program also includes the opportunity to develop appropriate data analysis systems. Examples include: estimating blood alcohol concentrations, reconstructing patterns of alcohol consumption, and monitoring large numbers of devices to identify significant, but infrequent, events while minimizing false positives.

031 Biomarkers for Alcohol-Induced Disorders

(Fast-Track proposals will be accepted.)

NIAAA is committed to the development of highly predictable, sensitive and reliable biomarkers for alcohol-induced disorders, including alcohol-induced organ damage and alcohol dependence. It is anticipated that new and novel biomarkers will be discovered and validated by using integrative global approaches in which unique molecular entities could be ascertained. For the biomarkers to be of clinical significance, it is essential that the tissues or samples used are easily obtainable. Sample collection and the assay must be relatively simple and accepted by the practitioners and patients. In addition, NIAAA is also interested in determining alcohol metabolites and adduct concentrations in tissues and organs after a single physiological dose, a large dose (e.g., binge drinking), and chronic consumption of alcohol. Determining the concentrations of FAEEs in brain, pancreas, heart, and other tissues after a single dose or chronic consumption is also encouraged. To accomplish these objectives, investigators are expected to employ state-of-the-art tools and technologies, including genomics, proteomics, metabolomics, and other biochemical procedures. New non-invasive imaging techniques are also envisioned as applicable to the identification of biomarkers for alcohol-induced diseases.

This solicitation is intended to promote the utilization of bioinformatics tools in an effort to integrate biological, clinical, and behavioral data for the identification of biomarkers that could be useful in the prognosis, diagnosis, and treatment of alcohol-induced tissue injury during the lifespan of individuals, including fetal development. New research studies focusing on the identification of early biomarkers of alcohol-induced tissue injury in well-defined patient populations are encouraged.

Phase I of the requested SBIR contract should be aimed at the feasibility of the study and initial identification of the potential biomarkers that are either direct products of ethanol oxidation or adducts of ethanol metabolites and/or cell constituents that are altered by alcohol exposure. Animal models and/or humans should be used for these studies. Fast-Track (combined Phase I and Phase II) proposals could be proposed. The Phase I component can be carried out using animal or human samples, but the Phase II component should concentrate on the validation of the identified biomarker(s) in human samples.

Some of the topics to be addressed under this program include, but are not limited to:

- Identification of biomarkers, either single molecules or combinations of them (biomarker signatures), for alcohol-induced organ damage (for liver, pancreas, lung, brain, etc) or alcohol dependence in blood or plasma and/or in other easily accessible tissues or employing non-invasive methods.

- Development and/or application of bioinformatic tools to mine the genomic, proteomic, metabolomic, and clinical and biological/behavioral data that will enable their integration at the system level.

032 Medications Development to Treat Alcohol Use Disorders and Alcohol Related Medical Disorders

(Fast-Track proposals will be accepted.)

Over the past decade, research on possible pharmacologic agents for treatment of excessive alcohol consumption has burgeoned. Drinking behavior is complex and appears to involve numerous neurotransmitter systems, including the opioid, serotonin, dopamine, GABA, and glutamate systems and various intercellular networks. Numerous medications interact with these neurotransmitter systems. Progress has also been made in elucidating the mechanisms of alcohol-induced organ damage. In order to obtain FDA approval, preclinical development with animal models and clinical development with humans must be conducted under FDA specifications. This contract is seeking proposals to help develop medications for the treatment of excessive alcohol consumption and alcohol-induced organ damage. Women and minorities should be included in the study.

SBIR Phase I of the requested contract should involve the development and early-phase preclinical and/or clinical testing of a specified medication for efficacy, toxicity, pharmacokinetics, formulation, and stability under Good Manufacturing Practice (GMP) or Good Laboratory Practice (GLP) conditions. The SBIR Phase II of the requested contract would involve larger-scale and more definitive studies to determine the efficacy, toxicology, pharmacokinetics, formulation, or stability under GMP or GLP conditions. Animal models and/or humans should be used. Positive findings from these studies may also be purchased by a pharmaceutical firm for further drug development.

033 Development of Methodology for Measuring and Enhancing Compliance for Medications

(Fast-Track proposals will be accepted.)

Currently, NIAAA is funding over 50 human pharmacotherapy studies. It appears that the effectiveness of medications is dependent, in part, on patient compliance. Measurement of patient compliance and remediation of compliance problems is challenging in both pharmacotherapy clinical trials and in medical practice. Current measurement methods employed include pill counts, electronic pillboxes, riboflavin, or other types of detectable markers incorporated into the medication and direct measurement of plasma levels of the medication. A number of remedies for noncompliance have been developed for research trials and applied with varying results, but little is known about the strategies used in clinical practice to enhance compliance. The purpose of this contract solicitation is to develop innovative methods for measuring and enhancing patient compliance to prescribed medication regimens. Either or both settings (research trials and/or clinical practice) may be addressed in the proposed research. Women and minorities should be included in the study.

The SBIR Phase I of the requested contract should entail development and early pre-clinical testing of the technique for measuring and enhancing compliance. The SBIR Phase II of the requested contract would involve larger-scale evaluations to determine the validity of the technique. This would involve measuring and enhancing compliance in the context of a double-blind, placebo-controlled pharmacologic trial, or clinical practice setting.

NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

NIDA's mission is to lead the nation in bringing the power of science to bear on drug abuse and addiction, through support and conduct of research across a broad range of disciplines and by ensuring rapid and effective dissemination and use of research results to improve prevention, treatment, and policy.

This solicitation invites proposals in the following areas:

090 Develop a Real-Time fMRI Feedback System that Allows Drug Abusers to Control their Cravings and Urges and/or Increase their Self-Control of their Drug Taking

(Fast-Track proposals will be accepted.)

It has recently been shown that pain patients, who are shown real-time feedback of their own brain activity as detected with fMRI, can control levels of brain activity in discrete brain regions. Further, these changes in brain activity were found to have a functional impact on the subjects, i.e. they were able to reduce the level of pain that they perceived.

Under this solicitation, we are seeking the development and demonstrated efficacy of a protocol for using fMRI to reduce drug abuse by allowing individuals to control the activity in specific brain areas associated with drug seeking. This technology could be used to help patients manage urges to take drugs by inhibiting the neural substrates associated with craving or drug seeking. Alternatively, this technology could be designed to allow patients to increase activity in areas of the brain associated with executive function and self-control, which, in turn, could help reduce or eliminate abuse of drugs. A combined approach would also be acceptable, where multiple brain areas are activated and/or inhibited by the subjects, with the goal of reducing or eliminating drug abuse. Lastly, an approach that reduces pain and the potential for drug abuse in patients receiving prescription pain medications is sought.

Phase I would involve developing this technology and testing the feasibility and efficacy of this technology in a pilot small study. Phase II would involve further development of those technologies that were successfully pilot tested in Phase I and the testing of those technologies in applied clinical settings.

091 Design and Synthesis of Treatment Agents for Drug Abuse

(Fast-Track proposals will be accepted.)

The purpose of this contract is to design and synthesize novel compounds intended specifically for the treatment of substance abuse including cocaine, methamphetamine or cannabinoid abuse. The classes of pharmacotherapeutic agents include, but are not limited to, compounds interacting with corticotrophins, cannabinoid, biogenic amines, GABA, and glutamate systems. The design and development of antibodies or vaccines as immunopharmacotherapy treatments for drug abuse will also be of interest.

In Phase I, the Contractor will design and synthesize new entities or modify and optimize existing lead compounds as potential treatment agents and carry out *in vitro* and/or *in vivo* pharmacological screens. In Phase II, the Contractor will perform pharmacological and toxicological evaluations and select lead compounds as potential clinical candidates.

093 Development of Website Training on Addiction Medicine for Pain Management Providers

(Fast-Track proposals will be accepted.)

Although there is evidence of the necessity to prevent/treat substance abuse when managing pain with opioids, the knowledge in this specific area of substance abuse and skills necessary for providing care for patients with co-morbid pain and a substance abuse problem has not been disseminated to the broader pain management community. 20 - 40% of patients on opioid therapy for chronic pain have co-morbid substance abuse problems. If the pain management provider does not have expertise in prevention/treatment of substance abuse/addiction, it will leave them unable to provide expert advice and care for patients with chronic pain and co-morbid substance abuse problems. Therefore, a cost-effective, scalable approach that will help clinicians in the assessment and management of pain patients at risk or active substance abuse/addiction is needed.

This SBIR project is to develop practical and efficacious web-based skills development training using advances in medical education such as simulated patients and role playing.

The developed training program must increase knowledge, improve attitudes and most importantly the ability of clinicians providing pain management to identify and treat patients with substance abuse problems. It would be desirable to include a validated instrument to screen for patients who are at risk of substance abuse/addiction and help them plan the treatment. The skills-development program must be easy to use by the target population and contain evidence based information. The interactive website should also be able to provide a connection between a clinician and a local addiction specialist. The website developer/provider should manage the process of obtaining appropriate review for providing

Continuing Medical Education (CME) and distribution of earned CME credits.

Phase I (six months): Provide formative research and evaluation of current evidence based resources considered for the content of the program. Provide in-depth evaluation of current technology and determine the feasibility of using an interactive web-based training program to increase clinicians' ability to effectively identify and manage patients with substance abuse and pain co-morbidity. Submit a summary report that includes the project plan for Phase II, delivery, methodology, system architecture and the contents of the training program.

Phase II (24 months): Design, build and test the usability, acceptance, and potential value of a working prototype among pain management providers. Develop and implement the full-scope training program that will be evaluated in a randomized trial.

Phase III: Product commercialization.

094 Development of Web-based Skills Training for Primary Care Physicians on Screening, Brief Intervention, Referral and Treatment

(Fast-Track proposals will be accepted.)

Primary care physicians (PCP) are at the forefront of identifying patients, including adolescents with substance abuse/addiction problems, ranging from licit drugs such as tobacco, alcohol, and prescription drugs, to illicit drugs such as cocaine, heroin, and marijuana. The prevalence of abuse of alcohol and illicit drugs in primary care has been estimated at 25% of patients. Most Americans see a PCP within a two-year period, providing the PCP the opportunity to participate in the public health goal of identifying and treating substance abuse. PCPs in general receive little if any training in the assessment and treatment of substance abuse in their patients. Numerous trials involving variety of patient populations have indicated that screening, brief intervention; referral can effectively address problems with substance abuse.

For example, SBIRT (Screening, Brief Intervention, and Referral to Therapy) is a recent research-to-practice advance in substance abuse treatment in primary care launched by the Center for Substance Abuse Treatment to expand treatment capacity. This involves the PCP implementing simple, practical, and office-based tools (such as the CAGE, TICS, ASSIST) to screen for substance abuse in their patients. Another example is CRAFFT test, a valid means of screening adolescents for substance-related problems and disorders. For patients who screen positive, the PCP delivers brief advice or intervention and referral depending on the severity of findings (at-risk use, abuse, and dependence).

This proposal will result in a scalable skills development program for PCPs that can be easily deployed in a manner convenient to the busy schedule of most PCPs. It will build from the experiences of SBIRT and other successful projects or programs, though, it is expected that this new web-based skills training will exceed efforts to date.

The goal of this contract concept is to develop practical and efficacious web-based skills development training using advances in medical education such as simulated patients and role playing.

The developed training program will increase knowledge, attitudes and, most importantly, ability of PCP to screen, intervene with and refer patients identified with at-risk use, abuse or dependence on psychoactive substances. The skills-development program must be easy to use by the target population and contain evidence-based information. The website developer/provider should manage the process of obtaining appropriate review for providing Continuing Medical Education (CME) and the distribution of earned CME credits. The interactive website should be also able to provide a connection between a PCP and a local specialized substance abuse treatment program.

Phase I (six months): Provide formative research and evaluation of current evidence based resources considered for the content of the program. Provide in-depth evaluation of current technology and determine the feasibility of using an interactive web-based training program to increase clinicians' ability to effectively identify and intervene with patients at-risk or that use, abuse or are dependent on psychoactive substances should be assessed. Submit a summary report that includes the project plan for Phase II, delivery, methodology, system architecture, and the contents of the training program

Phase II (24 months): Design, build and test the usability, acceptance, and potential value of working prototype among PCPs. Develop and implement the full-scope training program that will be evaluated in a randomized trial.

Phase III: Product commercialization.

095 Drug Abuse Screening, Assessment, Patient-Treatment Matching Technologies for Use in Primary Care

(Fast-Track proposals will be accepted.)

This initiative is intended to stimulate development of new technologies for drug abuse screening, assessment, and patient-treatment matching and HIV testing in primary care settings. Coordination between primary care and addiction testing treatment and HIV/AIDS testing and referral can facilitate provision of more holistic, integrated, and cost-effective health care for individuals with problem drug use, abuse, and related health problems, including HIV/AIDS. New screening and assessment instruments that are easily administered by a variety of health care providers are needed to detect problem drug use and related health problems among patients in primary care settings. NIDA is interested only in screens and assessments that are—or can be—embedded into comprehensive behavioral health screening/assessment instruments, in order to maximize efficiency and likelihood of use. These instruments should have optimal levels of sensitivity and specificity for their proposed purposes within primary care settings. New technologies have great potential for helping treatment providers in all settings (a) screen for problem drug use and associated health problems and risk behaviors, including HIV/AIDS; (b) assess the nature and degree of drug use and related disorders, and (c) identify appropriate types and levels of treatment services for patients based on their individual treatment needs. These new technologies can make more cost-effective the identification of problem drug use, HIV/AIDS and associated disorders in all health care settings, speeding the assessment process, and improving treatment placement decisions. Phase I would explore the feasibility of technological solutions for use in primary care settings for patient screening, assessment, and placement. Selected technical approaches would be developed and pilot tested. Phase II would involve further development of those technologies that were successfully pilot tested in Phase I and the testing of those technologies in applied primary care settings.

096 Tools to Measure Intervention Costs, Cost Effectiveness, and Net Economic Benefits

(Fast-Track proposals will be accepted.)

Most social programs, including substance abuse prevention programs, are asked to demonstrate efficacy, effectiveness, the reach of their program, or their ability to address identified needs of particular population subgroups. From a social policy perspective, it has become increasingly important to demonstrate to funders, agencies and a discerning public the extent to which programs designed to benefit youth and others do so at reasonable financial burden. This information is the subject of various types of economic evaluation including cost, cost-offset, cost-benefit, cost-effectiveness, and cost-utility analysis, fields of growing importance and concentration. Despite the important role economic evaluation can play in funding decisions, there are few analysis tools available to aid in these economic studies, and a dearth of research in the many areas of economic analysis that can help inform the public policy discourse about the value of evidence-based prevention efforts. This SBIR contract invites submissions to produce high quality, conceptually grounded, robust, and user-friendly tools to assess the full costs and direct economic benefits of prevention programs, the results of which can be used in economic evaluations of prevention programs. Studies can also address the net economic benefit of prevention interventions on substance use and related problems, as well as on their ability to mitigate health care and other service system burdens.

097 Development of Nanoscience-based Probes, Delivery Systems, and Therapies for Substance Use Disorders

(Fast-Track proposals will be accepted.)

Nanoscience and nanotechnology, by manipulating matter at the atomic or molecular levels, are emerging research areas that have the potential to fundamentally transform the study of biological systems and lead to the development of new methods for detection, prevention, and treatment of substance abuse and related disease states. NIDA invites nanotechnology-based proposals in the following areas:

A. Methods to enhance the efficacy of FDA-approved compounds by reducing their size to the nanoscale range to alter absorption, distribution, metabolism, or excretion.

B. Development of new compounds, through manipulation of matter at the atomic or molecular levels that could more readily pass the blood-brain-barrier or cell membranes.

C. Development of nanoscale particles for controlled targeted delivery of therapeutics, genes, or antibodies.

D. Expedited drug development through biomolecular analysis and characterization.

E. Application of nanostructures (e.g. noble metal nanoparticles, quantum dots, and nanolithographic structures that show promise for diagnostic development) for identification and analysis of genes, proteins, and other biological molecules implicated in the actions of drugs of abuse.

F. Improved imaging methods for identifying the location, distribution and site of action of drugs and drug-loaded nanoparticles in the brain.

Proposals are invited from any of the above areas. Phase I should demonstrate convincingly the viability of the proposed innovation, whereas Phase II should carry out the development, characterization, testing, and screening of the innovation.

098 Discovery and Study of Psychoactive Components of Botanicals

(Fast-Track proposals will be accepted.)

NIDA is looking for proposals to develop methods for the isolation, purification, identification and characterization of active and inactive ingredients of herbal plants (stimulants, hallucinogenic, analgesics, and/or narcotics) and evaluation of their biological properties. Such studies may include chemistry, toxicology, pharmacodynamics, pharmacokinetics and the mechanisms of action of active and inactive ingredients to understand their efficacy, usefulness, adverse effects and abuse potential.

Phase I should demonstrate the feasibility of the proposed innovation and Phase II, the development, characterization, testing, and screening of innovation.

NATIONAL INSTITUTE OF MENTAL HEALTH (NIMH)

The mission of the National Institute of Mental Health (NIMH) is to reduce the burden of mental illness through research on the mind, brain, and behavior. Mental disorders constitute an immense burden on the U.S. population, with major depression now the leading cause of disability in the U.S., and schizophrenia, bipolar disorder, and obsessive-compulsive disorder ranked among the ten leading causes of disability. NIMH also takes the lead in understanding the impact of behavior on HIV transmission and pathogenesis, and in developing effective behavioral preventive interventions. The NIMH conducts a wide range of research, research training, research capacity development, as well as, public information outreach and dissemination to fulfill its mission.

This solicitation invites proposals in the following areas:

059 Development and Evaluation of Tools to Enhance the Dissemination of Educational Information Intended Specifically for Autism Caregivers

(Fast-Track proposals will not be accepted.)

The Interagency Autism Coordinating Committee at the NIH, as well the FY04 Senate Report emphasize the need for the NIMH to support behavioral and clinical research related to autism spectrum disorders across the lifespan (e.g., including adults and older adults with the disorder) and to the needs of the families of these individuals. There is a large body of research literature on assisting caregivers to reduce stress and improve coping skills during the chronic illness of a family member (e.g., Alzheimer's Disease and other mental disorders). Currently, very little of this information has been translated into useful strategies for individuals who have family members with Autism.

The purpose of this contract is to develop and evaluate a suite of interactive tools that will provide educational and health related activities, and resources to caregivers of individuals with autism to help them manage day to day activities. The product should provide a variety of assistive information ranging from empirically based strategies for reducing caregiver stress to practical assistance and information (e.g., legal and education rights, long term care planning). In terms of practical assistance, special focus should be made on developmental transitions (e.g. a child starting elementary school, high school, or college, group home transitions, etc.), state and county allowances, approaches for meeting with school administrators, teachers, etc. During Phase I prototype curriculum, materials and strategies will be developed and evaluated by relevant stakeholders. As part of the proposal, the offeror can submit plans for adapting existing instruments to measure stress and coping, including symptoms of anxiety and depression. Proposed advisory boards should include the following

expertise: caregiving treatment and interventions in autism; life course and behavioral profiles of individuals with autism and their families; autism researchers; stakeholders. The small business should provide a plan for how this product will be maintained and updated after the contract ends.

The products created under this contract should be broadly disseminated. Therefore the offeror must recognize the diversity of families in terms of age, racial/ethnic minority status, socio-economic status, rural or other environmental factors, diversity of family types (e.g., family configuration) and special family situations that might impact training and research participation (e.g., mental health of other family members) and address specific ways these factors will be taken into consideration (e.g., focus groups). Phase I should be limited in scope, with a specific target population defined. Families should be recruited in order to obtain a representative sample of the overall stakeholder population. Content area should also be defined and tailored to the target problems; as well as contextual variables of the families (e.g., age, ethnicity, education level, rural/urban residence);

Two or three meetings with NIMH staff may be proposed for orientation and presentation of draft prototypes. Since the degree of complexity of this project may require more than six months to complete, the offeror should clearly identify the amount of time and support needed to complete their proposed scope of work. Up to one year of work would be allowed for a Phase I contract and up to $250,000 total costs/year. Phase II contracts would allow up to two years at up to $450,000 total costs/ year.

060 Multi-Media Training for Social Workers in Evidence-Based Mental Health Practices and Psychotherapies

(Fast-Track proposals will not be accepted.)

On April 12, 2007 the National Institute of Mental Health held a meeting titled: “Partnerships to Integrate Evidence-Based Mental Health Practices into Social Work Education and Research.” This meeting convened deans and directors of social work programs, faculty that teach evidence-supported mental health interventions in social work education, NIMH, SAMHSA and key national organizations. The purpose of the meeting was to facilitate the development of a coordinated strategy that would more directly prepare clinical social workers to apply and implement empirically supported mental health service strategies and interventions. There was consensus that while a number of important initiatives in EBP training currently exist in academic programs, the need for social workers prepared to deliver such interventions is not currently being met. One of the conclusions was that although there are a number of evidence-based therapies there are very few training packages/curricula specifically for clinical social workers. Highlighted in the discussion was the need for more investment in educational and training strategies that go beyond simple text books. This would include tools that can be implemented for continuing clinical education and for academic social work programs that train clinicians. One of the major barriers to disseminating and implementing psychotherapies is the lack of well-developed tools and programs (computer-based/video/cd rom/ train-the-trainers models or combinations of these models).

The purpose of this contract is to develop and evaluate a set of tools for training social work clinicians in evidence-based practices and/or psychotherapies in the context of “real-world”, standard practice for the profession. Under this topic, NIMH plans to support several (2-3) contracts focused on multi-media training for psychotherapies targeting, where indicated, specific populations (e.g. children, adults, geriatric, etc.) and geared toward varying levels of trainee-ship (e.g.: undergraduate, post-graduate, continuing education for established clinicians, etc.) .

During Phase I it is expected that the following will be developed and evaluated: (1) prototype training manuals and curriculum that are tailored to the specific needs of social work practitioners; (2) interactive programs designed to be adjunctive and/or stand alone modules (e.g., continuing education) to help train social work clinicians in delivering an established evidence based therapy/intervention ; (3) companion web-based support (e.g., on-line registration for credit, updates, help-desk, tests, resources for educators); (4) evaluation criteria (satisfaction, intent to use, knowledge, attitudes etc) and strategy for assessing the program/tools; (5) standards for certification and (6) the development of follow-up/ refresher training modules and their scheduling. It is essential that the training materials, educational courses and modes of delivery (classroom, internet, video, CD ROM etc) reflect the myriad types of clients and situations encountered in social work practice, particularly in the selection of interactive /standardized case based examples. Proposed Advisory Boards should reflect

expertise in areas related to adult learning, social work practice and education, social work consumers and individuals engaged in research on evidence based practices.

Two or three meetings with NIMH staff may be proposed for orientation and presentation of draft prototypes. Since the degree of complexity of this project may require more than six months to complete, the offeror should clearly identify the amount of time and support needed to complete their proposed scope of work. Up to one year of work would be allowed for a Phase I contract and up to $250,000 total costs/year. Phase II contracts would allow up to two years at up to $450,000 total costs/ year.

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

NATIONAL CENTER ON BIRTH DEFECTS AND DEVELOPMENTAL DISABILITIES (NCBDDD)

NCBDDD provides national leadership for preventing birth defects and developmental disabilities and for improving the health and wellness of people with disabilities.

This solicitation invites proposals for the following topic area:

007 Maximize Quality and Quantity of DNA from Mailed Cytobrushes

As part of the mission to prevent birth defects, NCBDDD has established the National Birth Defects Prevention Study (NBDPS), a multi-site, population-based case-control study to identify potential genetic and environmental risk factors for birth defects. The study includes ascertainment of case and control infants, maternal interviews, and collection of DNA from cheek cells using cytobrushes mailed to each mother, father, and infant. To identify potential genetic risk factors, CDC and collaborating sites have collected buccal-derived DNA samples for 9,140 case-infants, 10,465 case-infant mothers, 8,703 case-infant fathers, 3,346 control-infants, 3,377 control-infant mothers, and 2,802 control-infant fathers. DNA is extracted from self-collected cytobrushes and stored for later analysis. One problem encountered in the NBDPS is that the extracted DNA is sometimes of insufficient quality and quantity for use with current whole genome amplification (WGA) methods. WGA is necessary for high-throughput genotyping of buccal-derived DNA samples. Other projects that include self-collection of buccal samples using cytobrushes may be experiencing the same problem with less than optimal quality and quantity DNA.

Phase I will use mailed cytobrush samples that are not part of the NBDPS.

1. Develop a WGA method that provides optimal DNA quantities from mailed cytobrush samples, both new and existing.
2. Identify a feasible, innovative technology that allows laboratories to extract DNA of optimal quantity and quality on new samples collected from buccal brushes.

The new technology will increase the number of DNA samples that are of useable quality and quantity for further analyses.

The new technology will allow maximum utilization of existing biologic samples, minimize the intrusion on study participants, and save funds in biologic sample recollection cost.

COORDINATING OFFICE FOR TERRORISM PREPAREDNESS AND EMERGENCY RESPONSE (COTPER)

The Coordinating Office for Terrorism Preparedness and Emergency Response (COTPER; http://www.cdc.gov/maso/pdf/COTPERfs.pdf) has primary oversight and responsibility for all programs that comprise CDC's terrorism preparedness and emergency response portfolio. Through an all-hazards approach to preparedness that focuses on threats from natural, biological, chemical, nuclear, and radiological events, COTPER helps the nation prepare for and respond to urgent threats to the public's health. COTPER's mission is to prevent death, disability, disease and injury associated with urgent health threats by improving preparedness of the public health system, the healthcare delivery system and the public through excellence in science and services.

To carry out its mission, COTPER (1) fosters collaborations, partnerships, integration, and resource leveraging to increase the Centers for Disease Control and Prevention's (CDC) health impact and achieve population health goals; (2) provides strategic direction to support CDC's terrorism preparedness and emergency response efforts; (3) manages CDC-wide preparedness and emergency response programs; (4) maintains concerted emergency response operations—including the Strategic National Stockpile and the

Director's Emergency Operations Center; (5) communicates terrorism preparedness and emergency response activities to internal and external stakeholders.

This solicitation invites proposals in the following areas:

001 Environmental Monitoring Systems for Forward Placed Assets

There is a need for cost-effective methodologies to monitor temperature and environmental conditions in forward placed assets. This contract seeks to develop field-expedient technology including compliant stand-alone instrumentation and validation, to monitor the environmental conditions of stockpiled assets. The technology should be readily usable by staff in Federal, State and Local health departments or by disaster planners that require management of stockpile materials. Optimally, the systems developed should have low maintenance costs; costs should be documented. In addition, evaluation and validation of the systems and processes is required. The following is of particular interest:

- Development and evaluation of instrumentation systems for monitoring of environmental conditions for forward placed assets such as CHEMPACK and in the future, RADPACK.

IMMUNIZATION SAFETY OFFICE (ISO)

The Vaccine Technology (VAXTECH) unit of the Immunization Safety Office (ISO) works on a variety of technological initiatives, projects, consultations, and applied research and development to enhance the safety of immunization. A major focus is promoting safer, simpler, and swifter vaccine delivery methods to overcome the dangers and drawbacks of the conventional needle-syringe. (http://www.cdc.gov/od/science/iso/research_activties/vaxdev.htm).

Encouraged and prioritized for award are those proposals responsive to the following solicitations that have high potential for early affordability in developing countries, and would be adaptable anywhere for either high-speed, mass vaccination campaigns for disease control and prevention, as well as economical and convenient use in routine immunization clinics**.**

003 Novel or Enhanced Methods for Vaccination via the Respiratory Tract

Proposals are requested for new or improved methods to administer vaccines – especially attenuated, live virus ones -- via the respiratory tract. These should address one or more of the following: 1) Delivery techniques, carriers, and constructs, including but not limited to aerosols, dry powders and nasal sprays; 2) Improving the uptake or effectiveness of vaccines delivered by this route; 3) Improved evaluation of deposition of vaccines into the respiratory tract, including but not limited to computer simulation models and *in vitro* models; 4) Techniques to study such vaccines in animal models; and 5) Sustainable power systems for respiratory devices in developing countries without requiring outlet (mains) electricity. Proposals are encouraged which focus on a specific vaccine in combination with a respiratory delivery approach and include a vaccine manufacturer as either the prime contractor, if SBIR-qualified, or as a subcontractor or collaborator.

004 Novel or Enhanced Methods for Cutaneous Vaccination

Proposals are requested for new or improved methods to deliver vaccine into the skin, by deposition, diffusion, or otherwise into any of its immunoactive tissues such as the epidermis and/or dermis. Proposals should address: 1) Delivery systems and antigen carriers for vaccines, including but not limited to the use of patches, minineedles, microneedles, microtines, powders, and/or the use of mechanical, electromagnetic, photonic, sonic, ballistic, chemical, or other energy forms to allow antigen to pass through the barrier of the stratum corneum. Proposals are encouraged which focus on a specific vaccine via the cutaneous route, and include a vaccine manufacturer as either the prime contractor, if SBIR-qualified, or as a subcontractor or collaborator.

005 Novel or Enhanced Methods for Vaccination by Jet Injection

Proposals are invited for new or improved disposable-cartridge jet injector technology for vaccination into intramuscular (IM), subcutaneous (SC), and/or intradermal (ID) tissues. Proposals may be for injectors or their associated technologies, such as auto-disabling cartridges, end-user filling systems and accessories, auto-reconstitution of lyophilized vaccines, and other related or useful components.

HUMAN SUBJECTS RESEARCH GUIDANCE AND INFORMATION SUPPLEMENT

PREPARING THE HUMAN SUBJECTS RESEARCH SECTION OF THE RESEARCH PLAN

In the Human Subjects Research section of the Research Plan, you must provide sufficient information for reviewers to determine that the proposed research meets (1) the requirements of the HHS regulations to protect human subjects from research risks (45 C.F.R. Part 46), (2) the requirements of NIH policies for data and safety monitoring of clinical trials, and (3) the requirements of NIH policies on inclusion of women, minorities, and children. See Instructions Pertaining to Non-Exempt Human Subjects Research.

If the research is exempt from the requirements in the Federal regulations, you must provide a justification for the exemption with sufficient information about the involvement of the human subjects to allow a determination by peer reviewers and NIH staff that claimed exemption(s) is/are appropriate. See Exempt Human Subjects Research.

Proposals must comply with this requirement; if not, proposal processing may be delayed or the proposal may be returned to the offeror without review.

For all research involving human subjects, a part of the peer review process will include careful consideration of protections from research risks, as well as the appropriate inclusion of women, minorities, and children. The Scientific Review Group (SRG) will assess the adequacy of safeguards of the rights and welfare of research participants, and the appropriate inclusion of women, minorities, and children, based on the information in the proposal.

To assist you in completing the Human Subjects Research portion of the Research Plan, we have provided six possible scenarios. All research will fall into one of these six scenarios. Determining which scenario best matches your proposed research depends on your answers to the following five questions:

Question 1: Does your proposed research involve human subjects?

Question 2: Does your proposed human subjects research meet the criteria for one or more of the exemptions in the HHS regulations (45 C.F.R. Part 46)?

Question 3: Does your proposed research meet the definition of clinical research?

Question 4: Does your proposed research include a Clinical Trial?

Question 5: Does your proposed research meet criteria for an NIH-Defined Phase III Clinical Trial?

Click on the questions and when you can answer the five questions, select the scenario that best matches your responses, and then follow the instructions provided for the scenario you choose.

DECISION TABLE FOR HUMAN SUBJECTS RESEARCH, PROTECTION AND THE INCLUSION OF WOMEN, MINORITIES, AND CHILDREN

	Criteria and Answers to Questions 1 thru 5				
Scenarios with linked instructions	1. Human Subjects Research	2. Exempt from HHS Human Subjects Regulations	3. Clinical Research	4. Clinical Trial	5. NIH-Defined Phase III Clinical Trial
A No Human Subjects	No	N/A	N/A	N/A	N/A
Requirements for Scenario A: If Human Subjects is "Yes," see Scenarios B-F below.					
B Human Subjects/E-4	Yes	Yes Exemption: 4	No	N/A	N/A
Requirements for Scenario B: - Indicate Exemption 4 (E-4) and include justification that E-4 is appropriate.					
C Human Subjects/ Other Exemptions	Yes	Yes Exemptions: 1, 2, 3, 5, 6	Yes	N/A	N/A
Requirements for Scenario C: - Indicate Exemption number(s) and include justification that the designated exemption(s) is appropriate. - Address "Inclusion of Women and Minorities" - Address "Inclusion of Children"					
D Clinical Research	Yes	No	Yes	No	N/A
Requirements for Scenario D: - Address Protection of Human Subjects - Address "Inclusion of Women and Minorities" - Address "Inclusion of Children" "Targeted/Planned Enrollment Table(s)" for each new study/ protocol (New proposals; Competing Renewal proposals; Competing Revisions) - "Inclusion Enrollment Report Table(s)" (Competing Renewals; Competing Revisions)					
E Clinical Trials	Yes	No	Yes	Yes	No
Requirements for Scenario E: - All requirements in Scenario D - Data and Safety Monitoring Plan - Note: Some trials may require a Data and Safety Monitoring Board, based on risk					
F NIH-Defined Phase III Clinical Trial	Yes	No	Yes	Yes	Yes
Requirements for Scenario F: - All requirements in Scenario E Increased requirements for Inclusion of Women and Minorities in Clinical Research					

HUMAN SUBJECTS RESEARCH

Question 1: Does your proposed research involve human subjects?

The first thing you must determine is whether or not your research involves human subjects, either at the applicant organization or at any other performance site or collaborating institution (e.g., subcontractors, consultants).

The research described in your proposal may include more than one research project; thus the proposal may include individual projects that meet the requirements for non-exempt or exempt human subjects research, or are not defined as human subjects research.

If research activities involving human subjects are planned at any time during the proposed project period, either at the applicant organization or at any other performance site or collaborating institution, then your answer is "Yes" even if the research is exempt from regulations for the protection of human subjects.

The HHS regulations "Protection of Human Subjects" (45 C.F.R. 46, administered by OHRP) define a *human subject* as a living individual about whom an *investigator* conducting *research obtains*:

- data through *intervention* or *interaction* with the individual or
- *identifiable private information*

Investigator: The OHRP considers the term investigator to include anyone involved in conducting the research. OHRP does not consider the act of solely providing coded private information or specimens (for example, by a tissue repository) to constitute involvement in the conduct of the research. However, if the individuals who provide *coded* information or specimens also collaborate on other activities related to the conduct of the research with the investigators who receive such information or specimens, they will be considered to be involved in the conduct of the research. [OHRP's Coded Specimen Guidance]

Research: HHS regulations define *research* at 45 C.F.R. 46.102(d) as follows:
Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

Obtains: In its guidance for use of coded specimens, OHRP has determined that under the definition of human subject at 45 C.F.R. 46.102(f), *obtaining* identifiable private information or identifiable specimens for research purposes constitutes human subjects research. *Obtaining* means receiving or accessing identifiable private information or identifiable specimens for research purposes. OHRP interprets *obtaining* to include an investigator's use, study, or analysis for research purposes of *identifiable private information* or identifiable specimens already in the possession of the investigator.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. (45 C.F.R. 46.102(f))

Interaction includes communication or interpersonal contact between investigator and subject. (45 C.F.R. 46.102(f))

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record). Private information must be *individually identifiable* (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. (45 C.F.R. 46.102(f))

Individually Identifiable Private Information: According to its guidance for use of coded specimens, OHRP generally considers private information or specimens to be *individually identifiable* as defined at 45 C.F.R. 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through *coding* systems. Conversely, OHRP considers private information or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Research Using Human Specimens or Data:

Regulatory requirements (Federal and state) to protect human subjects apply to a much broader range of research than many investigators realize, and researchers using *human specimens and/or data* are often unsure about how regulations apply to their research. Regulatory obligations to protect human subjects would apply, for example, to research that uses –

- Bodily materials, such as cells, blood or urine, tissues, organs, hair or nail clippings, from living individuals who are individually identifiable to the investigator(s), even if these materials were collected by others;
- Residual diagnostic specimens from living individuals that are individually identifiable to the investigator(s), including specimens obtained for routine patient care that would have been discarded if not used for research;
- Private information, such as medical information, about living individuals that is individually identifiable to the investigator(s), even if the information was not specifically collected for the study in question. This includes research on genetic information that can be readily associated by the investigator(s) with identifiable living individuals.

The definition of "human subject" includes, but is not limited to, human organs, tissues, and body fluids from living individuals, as well as private graphic, written, or recorded information about living individuals, if (1) there is interaction or intervention with a living individual to obtain the specimens or data for research purposes, or (2) the identity of the subjects can be readily ascertained by the investigator or other members of the research team.

Research that involves only *coded* private information/data or coded human biological specimens may not constitute human subjects research under the HHS human subjects regulations (45 C.F.R. Part 46) if:

- the specimens and/or private information were not collected specifically for the currently proposed research project through an interaction/intervention with living individuals AND
- the investigator(s) (including collaborators) on the proposed research cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain (e.g., the researcher's access to subject identities is prohibited by written repository procedures and policies and/or through an agreement signed between the recipient researcher and the repository providing the specimens and/or data). [See definitions below and the following guidance from the Office for Human Research Protections (OHRP) for additional information and examples: http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf.]

Individuals who provide *coded* information or specimens for proposed research and who also collaborate on the research involving such information or specimens are considered to be involved in the conduct of human subjects research.

Coded: With respect to private information or human biological specimens, *coded* means that:

(1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol or combination thereof (i.e., the code); and

(2) a key to decipher the code exists, enabling linkage of the identifying information with the private information or specimens.

You may find it helpful to consult the following guidance from OHRP:

- OHRP Decision Charts: http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm
- OHRP Policy on Coded Specimens and Data: http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf
- OHRP Guidance on Repositories: http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm; http://www.hhs.gov/ohrp/humansubjects/guidance/guid1223.pdf

With regard to the engagement of performance sites in proposed human subjects research, you may find it helpful to consult the following:

- OHRP Memo on Engagement: http://www.hhs.gov/ohrp/humansubjects/assurance/engage.htm

The decisions about when research involving human specimens and/or data from subjects is considered human subjects research are complex. The OHRP recommends that institutions have policies in place that designate the individual or entity authorized to determine whether proposed research is exempt from regulatory requirements to protect human subjects and that determinations should be made by someone other than the investigator.

You need to be aware that the involvement of human subjects in non-exempt research must be approved by your IRB prior to award.

The NIH Office of Extramural Research Human Subjects website contains additional information and Frequently Asked Questions that may help investigators understand how these regulations and Guidance documents apply to their research. See http://grants.nih.gov/grants/policy/hs/index.htm.

How can you determine whether research that involves only the use of specimens and/or data from pathology archives or a specimen bank and/or data repository is human subjects research?

The research described in your proposal may include more than one research project; thus the proposal may include separate projects that meet the requirements for either human subjects research, exempt human subjects research, or are not defined as human subjects research. Examples are provided below:

- If the specimens and/or data were obtained specifically for the currently proposed research project through intervention or interaction with a living individual, then your research is human subjects research.
- If you receive or have access to individually identifiable specimens or data from living individuals (e.g., pathology or medical records), your proposed research is human subjects research.
- If you receive or have access to existing individually identifiable private information or identifiable specimens from living individuals (e.g., pathology or medical records), but you as the investigator or your collaborator record the information in such a manner that you cannot subsequently access or obtain direct or indirect identifiers that are linked to the subjects the research project that you conduct using data recorded in this manner meets the requirements of Exemption 4. If you will retain or can access any identifiers, the research project is not exempt under Exemption 4.
- If you are using specimens and/or data and neither you nor your collaborators can identify the subjects from whom the specimens and/or data were obtained either directly or indirectly through coding systems, the HHS human subjects regulations (45 C.F.R. Part 46) do not apply at all.
- If your research involves only coded private information/data or coded specimens, OHRP does not consider this research to involve human subjects as defined under the HHS Protection of Human Subjects Regulations (45 C.F.R. Part 46.102(f)) *if* the following conditions are *both* met:
    - the private information/data or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; *and*
    - the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:

(a) the key to decipher the code is destroyed before the research begins;

(b) the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased;

(c) there are IRB approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; *or*

(d) there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

What is not human subjects research under HHS regulations at 45 C.F.R. Part 46?

- Research that does not involve intervention or interaction with living individuals, or identifiable private information is not human subjects research (see definitions),
- Research that only proposes the use of cadaver specimens is not human subjects research, because human subjects are defined as "living individuals." The use of cadaver specimens is not regulated by 45 C.F.R. Part 46, but may be governed by other federal, state and local laws.

Guidance and Additional Instructions

If you answered "No" to Question 1, then proceed to Scenario A.

If you answered "Yes" to Question 1, then you may need to determine whether your research meets the criteria for an exemption from the Human Subjects Protection requirements. Proceed to Question 2.

If you need to consider an alternative scenario, return to the Decision Table.

EXEMPT HUMAN SUBJECTS RESEARCH

Question 2: Does your proposed human subjects research meet the criteria for one or more of the exemptions in the HHS regulations (45 C.F.R. 46)?

Some human subjects research is exempt from the HHS regulations (45 C.F.R. 46). OHRP guidance states that Exemptions should be independently determined (http://www.hhs.gov/ohrp/humansubjects/guidance/irb71102.pdf). Institutions often designate their IRB to make this determination. Because NIH does not require IRB approval at time of proposal, the exemptions designated in item 4a often represent the opinion of the PI, and the justification provided for the exemption by the PI is evaluated during peer review.

The research described in your proposal may include more than one research project; thus the proposal may include individual projects that meet the requirements for non-exempt or exempt human subjects research, or are not defined as human subjects research.

If research activities involving human subjects are planned at any time during the proposed project period, either at the applicant organization or at any other performance site or collaborating institution, then your answer is "Yes" to Question 1 "Does your proposed research involve human subjects" even if the research is exempt from regulations for the protection of human subjects.

Research involving individuals who are or who become prisoners cannot be exempt under any exemption categories (see 45 CRF Part 46 Subpart C).

Your human subjects research is exempt if all of the proposed research meets the criteria for one or more of the following six exemptions.

Exemption 1: Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

Exemption 2: Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless:

(i) information obtained is recorded in such a manner that human subjects can be identified directly or through identifiers linked to the subjects and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

Exemption 2 for research involving survey or interview procedures or observation of public behavior, does not apply to research with children (see 45 CF. Part 46 Subpart D), except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

Exemption 3: Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

Exemption 4: Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

The humans subjects regulations decision charts (http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm) from the Office of Human Research Protection (OHRP) will help you to see whether your research falls under the human subjects regulations and if so, whether it meets the criteria for Exemption 4. See also the information contained at: Exemption 4 Guidance and Information.

The NIH Office of Extramural Research website also contains information that is helpful for determining whether your human subjects research meets the criteria for Exemption 4. See http://grants.nih.gov/grants/policy/hs/index.htm.

Research that meets the criteria for Exemption 4 is not considered "clinical research" as defined by NIH. Therefore the NIH policies for inclusion of women, minorities and children in clinical research do not apply to research projects covered by Exemption 4.

Exemption 5: Research and demonstration projects that are conducted by or subject to the approval of Department or Agency heads and that are designed to study, evaluate, or otherwise examine: (i) public benefit or service programs (ii) procedures for obtaining benefits or services under those programs (iii) possible changes in or alternatives to those programs or procedures or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

Exemption 6: Taste and food quality evaluation and consumer acceptance studies (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Guidance and Additional Instructions

If you answered "Yes" to Question 2, then your research meets the criteria for an exemption.

- If your research meets the criteria for Exemption 4, then follow the instructions for Scenario B and read the information contained in Exemption 4 Guidance and Information.
- If your research meets the criteria for any of the other five exemptions, follow the instructions for Scenario C.

Remember that you need to identify which exemption(s) you believe is applicable to your research, and provide a justification for the exemption(s) with sufficient information about the involvement of human subjects to allow a determination by peer reviewers and NIH staff that the claimed exemption(s) is appropriate.

If you answered "No" to Question 2, then your research does not qualify for one of the exemptions, and your research is not exempt from full IRB review. Proceed to Question 3.

If you need to consider an alternative scenario, return to the Decision Table.

CLINICAL RESEARCH

Question 3: Does your proposed research meet the definition of clinical research?

The NIH defines Clinical Research as:

(1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies.

(2) Epidemiologic and behavioral studies.

(3) Outcomes research and health services research.

Clinical research that does not meet the criteria for a clinical trial or an NIH-defined Phase III clinical trial must follow the instructions in Scenario D.

Research projects that meet the criteria for Exemption 4 are not considered "clinical research." Investigators who propose research that meets the criteria for Exemption 4 must follow the instructions provided in Scenario B.

Guidance and Additional Instructions

If you answered "Yes" to Question 3, then proceed to Question 4 and Question 5 to determine whether your research meets the criteria for a clinical trial or an NIH-defined Phase III clinical trial.

If you answered "No," then you need to consider an alternative scenario. Return to the Decision Table.

CLINICAL TRIAL

Question 4: Does your proposed research include a clinical trial?

The NIH defines a *clinical trial* as a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective.

Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits these criteria of a clinical trial.

Human subjects research to develop or evaluate clinical laboratory tests (e.g. imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test will be used for medical decision-making for the subject or the test itself imposes more than minimal risk for subjects.

Biomedical clinical trials of experimental drug, treatment, device or behavioral intervention may proceed through four phases:

Phase I clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range, and to identify side effects).

Phase II clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.

Phase III studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.

Phase IV studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

Guidance and Additional Instructions

If you answered “Yes” to Question 4, then you will need to provide a general description of a Data and Safety Monitoring Plan. See Scenario E.

Also continue to Question 5 to determine whether your research meets the criteria for an NIH-defined Phase III clinical trial.

If you answered “Yes” to Question 3 (Clinical Research) and “No” to Question 4 (Clinical Trial), then follow the instructions for Scenario D.

If you answered “No” to Question 4, you will need to consider an alternative scenario. Return to the Decision Table.

NIH-DEFINED PHASE III CLINICAL TRIAL

Question 5: Does your proposed research meet criteria for an NIH-Defined Phase III Clinical Trial?

An *NIH-Defined Phase III Clinical Trial* is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of either evaluating an experimental intervention in comparison with a standard or control intervention or of comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

If your research meets the above criteria, then in addition to providing a Data and Safety Monitoring Plan, you will be expected to address whether you expect to find clinically important sex/gender and/or race/ethnicity differences in the intervention effect. The discussion may include supporting evidence and/or data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology, and other relevant studies.

You will be expected to provide a research plan that must include one of the following plans:

- Plans to conduct valid analyses to detect significant differences in intervention effect among sex/gender and/or racial/ethnic subgroups when prior studies strongly support these significant differences among subgroups, OR
- Plans to include and analyze sex/gender and/or racial/ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups. (Representation of sex/gender and racial/ethnic groups is not required as subject selection criteria, but inclusion is encouraged.), OR
- Plans to conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect between subgroups.

Guidance and Additional Instructions

If you answered “Yes” to Question 5, then follow the instructions for Scenario F.

If you answered “No,” then you need to consider an alternative scenario. Return to the Decision Table.

EXEMPTION 4 GUIDANCE AND INFORMATION

Research that meets the criteria for Exemption 4 is Human Subjects Research but it is not considered clinical research.

Exemption 4 includes research projects involving the collection or study of *existing* data, documents, records, pathological specimens, or diagnostic specimens, if these sources are *publicly available* or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through *identifiers* linked to the subjects.

What is meant by "existing" data or specimens?

Exemption 4 applies to retrospective studies of specimens and/or data that have already been collected. The materials must be "on the shelf" (or in the freezer) at the time the protocol is submitted to the IRB or other designated officials at your institution to determine whether the research is indeed exempt. Research that involves the ongoing collection of specimens and/or data does not meet the criteria for Exemption 4.

What is meant by "publicly available sources"?

This language in the regulation was intended to apply to public sources of data, such as census data. Its meaning with respect to human tissue specimens is widely debated. Although there are organizations that make human cells and tissues broadly accessible to the research community, these materials are not usually available to the public at large and are not generally considered to be publicly available.

What is meant by "identifiers linked to the subjects"?

Identifiers, such as names, social security numbers, medical record numbers, or pathology accession numbers, or other codes that permit specimens to be linked to living individuals and perhaps also to associated medical information.

How can I determine whether my research meets the criteria for Exemption 4?

The humans subjects regulations decision charts (http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm) from the Office of Human Research Protection (OHRP) will help you to see whether your research falls under the human subjects regulations and if so, whether a research project meets the criteria for Exemption 4.

OHRP advises that investigators should not have the authority to make an independent determination that research involving human subjects is exempt. OHRP guidance states that Exemptions should be independently determined (http://www.hhs.gov/ohrp/humansubjects/guidance/irb71102.pdf). Institutions often designate their IRB to make this determination. Because NIH does not require IRB approval at time of proposal, the exemptions designated in item 4a often represent the opinion of the Principal Investigator, and the justification(s) provided by the Principal Investigator for the exemption(s) is/are evaluated during peer review.

Information is also available on the NIH Office of Extramural Research website at http://grants.nih.gov/grants/policy/hs/index.htm.

How can you determine whether research that involves only the use of specimens and/or data from pathology archives or a specimen bank and/or data repository is human subjects research?

The research described in your proposal may include more than one research project; thus the proposal may include separate projects that meet the requirements for either human subjects research, exempt human subjects research, or are not defined as human subjects research. Examples are provided below:

- If the specimens and/or data were obtained specifically for the currently proposed research project through intervention or interaction with a living individual, then your research is human subjects research.
- If you receive or have access to individually identifiable specimens or data from living individuals (e.g., pathology or medical records), your proposed research is human subjects research.
- If you receive or have access to existing individually identifiable private information or identifiable specimens from living individuals (e.g., pathology or medical records), but you as the investigator or your collaborator record the information in such a manner that you cannot subsequently access or obtain direct or indirect identifiers that are linked to the subjects the research project that you conduct using data recorded in this manner meets the requirements of Exemption 4. If you will retain or can access any identifiers, the research project is not exempt under Exemption 4.
- If you are using specimens and/or data and neither you nor your collaborators can identify the subjects from whom the specimens and/or data were obtained either directly or indirectly through coding systems, the HHS human subjects regulations (45 C.F.R. Part 46) do not apply at all.
- If your research involves only coded private information/data or coded specimens, OHRP does not consider this research to involve human subjects as defined under the HHS Protection of Human Subjects Regulations (45 C.F.R. Part 46.102(f)) *if* the following conditions are *both* met:
    - the private information/data or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; *and*
    - the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
        (a) the key to decipher the code is destroyed before the research begins;
        (b) the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased;
        (c) there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; *or*
        (d) there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

Guidance and Additional Instructions

If your research meets the criteria for Exemption 4, refer to Scenario B.

If you need to consider an alternative scenario, return to the Decision Table.

INSTRUCTIONS PERTAINING TO NON-EXEMPT HUMAN SUBJECTS RESEARCH

In your proposal narrative, create a section entitled “E. Human Subjects Research” immediately following the last entry in the Research Design and Methods section. Although no specific page limitation applies to this section of the proposal, be succinct. Scientific Review Groups will assess each proposal as being “acceptable” or “unacceptable” with regard to the protection of human subjects.

As the first entry, create a heading entitled “Protection of Human Subjects.” Use subheadings to address the issues listed under items 1-4 below.

If your research includes a clinical trial, address item 5. "Data and Safety Monitoring Plan."

Protection of Human Subjects

1. RISKS TO THE SUBJECTS

a. ***Human Subjects Involvement and Characteristics***

- Describe the proposed involvement of human subjects in the work outlined in the Research Design and Methods section.
- Describe the characteristics of the subject population, including their anticipated number, age range, and health status.
- Identify the criteria for inclusion or exclusion of any subpopulation.
- Explain the rationale for the involvement of special classes of subjects, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations. Note that 'prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers) as well as subjects who become incarcerated after the study begins.
- List any collaborating sites where human subjects research will be performed, and describe the role of those sites in performing the proposed research.

b. ***Sources of Materials***

- Describe the research material obtained from living human subjects in the form of specimens, records, or data.
- Describe any data that will be recorded on the human subjects involved in the project.
- Describe the linkages to subjects, and indicate who will have access to subject identities.
- Provide information about how the specimens, records, or data are collected and whether material or data will be collected specifically for your proposed research project.

c. ***Potential Risks***

- Describe the potential risks to subjects (physical, psychological, social, legal, or other), and assess their likelihood and seriousness to the subjects.
- Where appropriate, describe alternative treatments and procedures, including the risks and benefits of the alternative treatments and procedures to participants in the proposed research.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. ***Recruitment and Informed Consent***

- Describe plans for the recruitment of subjects (where appropriate) and the process for obtaining informed consent. If the proposed studies will include children, describe the process for meeting requirements for parental permission and child assent.

- Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. Informed consent document(s) need not be submitted to the PHS agencies unless requested.

b. ***Protection Against Risk***

- Describe planned procedures for protecting against or minimizing potential risks, including risks to confidentiality, and assess their likely effectiveness.

- Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Studies that involve clinical trials (biomedical and behavioral intervention studies) must include a description of the plan for data and safety monitoring of the research and adverse event reporting to ensure the safety of subjects.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

- Discuss the potential benefits of the research to the subjects and others.

- Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and others.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

- Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.

- Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

NOTE: Test articles (investigational new drugs, devices, or biologicals) including test articles that will be used for purposes or administered by routes that have not been approved for general use by the Food and Drug Administration (FDA) must be named. State whether the 30-day interval between submission of applicant certification to the FDA and its response has elapsed or has been waived and/or whether use of the test article has been withheld or restricted by the Food and Drug Administration, and/or the status of requests for an IND or IDE covering the proposed use of the test article in the research plan.

5. DATA AND SAFETY MONITORING PLAN

- If your research includes a clinical trial, create a section heading entitled "Data and Safety Monitoring Plan."

- Provide a general description of a monitoring plan that you plan to establish as the overall framework for data and safety monitoring. Describe the entity that will be responsible for monitoring and the process by which Adverse Events (AEs) will be reported to the Institutional Review Board (IRB), the funding I/C, the NIH Office of Biotechnology Activities (OBA), and the Food and Drug Administration (FDA) in accordance with Investigational New Drug (IND) or Investigational Device Exemption (IDE) regulations. Be succinct. Contact the FDA (http://www.fda.gov) and also see the following websites for more information related to IND and IDE requirements:

http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr312_01.html (IND)
http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr812_01.html (IDE)

- The frequency of monitoring will depend on potential risks, complexity, and the nature of the trial; therefore, a number of options for monitoring trials are available. These can include, but are not limited to, monitoring by a:

  a. Principal Investigator (required)

  b. Independent individual/Safety Officer

  c. Designated medical monitor

  d. Internal Committee or Board with explicit guidelines

  e. Data and Safety Monitoring Board (DSMB). NIH specifically requires the establishment of *Data and Safety Monitoring Boards* (DSMBs) for *multi-site* clinical trials involving interventions that entail potential *risk* to the participants, and generally for Phase III clinical trials. Although Phase I and Phase II clinical trials may also use DSMBs, smaller clinical trials may not require this oversight format, and alternative monitoring plans may be appropriate.

  f. Institutional Review Board (IRB - required)

- A detailed Data and Safety Monitoring Plan must be submitted to the applicant's IRB and subsequently to the funding IC for approval prior to the accrual of human subjects (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html). For additional guidance on creating this Plan, see the above reference.

Guidance and Additional Instructions

Proceed to Inclusion of Women and Minorities.

INCLUSION OF WOMEN AND MINORITIES

Create a section heading entitled "Inclusion of Women and Minorities" and place it immediately following the “Protection of Human Subjects” section. Although no specific page limitation applies to this section of the proposal, be succinct.

Scientific Review Groups will assess each proposal as being “acceptable” or “unacceptable” with regard to the protection of human subjects.

In this section of the Research Plan, address, at a minimum, the following four points:

1. The targeted/planned distribution of subjects by sex/gender and racial/ethnic groups for each proposed study or protocol using the format in the Targeted/Planned Enrollment Table. (Instructions for completing this table are provided below.) If you are using existing specimens and/or data that does not meet the criteria for Exemption 4 and you do not have access to information on the distribution of women and minorities, so state and explain the impact on the goals of the research as part of the rationale that inclusion is inappropriate (item 3 below). Alternatively, you may describe the women and minority composition of the population base from whom the specimens and/or data will be obtained. Include the Targeted/Planned Enrollment Table (MS Word or PDF) in this section.
2. A description of the subject selection criteria and rationale for selection of sex/gender and racial/ethnic group members in terms of the scientific objectives and proposed study design. The description may include, but is not limited to, information on the population characteristics of the disease or condition under study.
3. A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group (see examples below).
4. A description of proposed outreach programs for recruiting sex/gender and racial/ethnic group members as subjects.

Examples of acceptable justifications for exclusion of:

A. ***One gender:***

1. One gender is excluded from the study because:

- inclusion of these individuals would be inappropriate with respect to their health;
- the research question addressed is relevant to only one gender;
- evidence from prior research strongly demonstrates no difference between genders;
- sufficient data already exist with regard to the outcome of comparable studies in the excluded gender, and duplication is not needed in this study.

2. One gender is excluded or severely limited because the purpose of the research constrains the applicant's selection of study subjects by gender (e.g., uniquely valuable stored specimens or existing datasets are single gender; very small numbers of subjects are involved; or overriding factors dictate selection of subjects, such as matching of transplant recipients, or availability of rare surgical specimens).
3. Gender representation of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens, or data-sets with incomplete gender documentation are used), and this does not compromise the scientific objectives of the research.

B. ***Minority groups or subgroups:***

1. Some or all minority groups or subgroups are excluded from the study because:

- Inclusion of these individuals would be inappropriate with respect to their health;
- The research question addressed is relevant to only one racial or ethnic group;

- Evidence from prior research strongly demonstrates no differences between racial or ethnic groups on the outcome variables;
- A single minority group study is proposed to fill a research gap;
- Sufficient data already exists with regard to the outcome of comparable studies in the excluded racial or ethnic groups and duplication is not needed in this study.

2. Some minority groups or subgroups are excluded or poorly represented because the geographical location of the study has only limited numbers of these minority groups who would be eligible for the study, and the investigator has satisfactorily addressed this issue in terms of:

- The size of the study;
- The relevant characteristics of the disease, disorder or condition;
- The feasibility of making a collaboration or consortium or other arrangements to include representation.

3. Some minority groups or subgroups are excluded or poorly represented because the purpose of the research constrains the applicant's selection of study subjects by race or ethnicity (e.g., uniquely valuable cohorts, stored specimens or existing datasets are of limited minority representation, very small numbers of subjects are involved, or overriding factors dictate selection of subjects, such as matching of transplant recipients or availability of rare surgical specimens).
4. Racial or ethnic origin of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens or data sets with incomplete racial or ethnic documentation are used) and this does not compromise the scientific objectives of the research.

Additional Instructions and Requirements When NIH-Defined Phase III Clinical Trials Are Proposed

If your proposed research includes an NIH-Defined Phase III Clinical Trial, the section on Inclusion of Women and Minorities also must address whether you expect to find clinically important sex/gender and/or race/ethnicity differences in the intervention effect. The discussion may include supporting evidence and/or data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology and other relevant studies. Your discussion of expected sex/gender and/or race/ethnicity differences in intervention effect must include selection and discussion of one of the following analysis plans:

- Plans to conduct valid analyses to detect significant differences in intervention effect among sex/gender and/or racial/ethnic subgroups when prior studies strongly support these significant differences among subgroups, *or*
- Plans to include and analyze sex/gender and/or racial/ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups. (Representation of sex/gender and racial/ethnic groups is not required as subject selection criteria, but inclusion is encouraged.), *or*
- Plans to conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect between subgroups.

Instructions for Completing the Targeted/Planned Enrollment Tables for Reporting Race and Ethnicity Data for Subjects in Clinical Research

A. New Proposals and Clinical Research Studies begun after January 10, 2002:

All new clinical research studies should collect and report information on participants with respect to two categories of ethnicity and five categories of race. The new Inclusion Enrollment Report Table (MS Word or PDF) for reporting summary data on participants to NIH includes two categories of ethnicity and five categories of race and is based on recent changes by the Office of Management and Budget (OMB) regarding standards for data on race and ethnicity. Investigators should review the instructions and Frequently Asked Questions about using the new Enrollment Table format at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html.

When reporting these data in the aggregate, investigators should report: (a) the number of respondents in each ethnic category; (b) the number of respondents who selected only one category for each of the five racial categories; (c) the total number of respondents who selected multiple racial categories reported as the "number selecting more than one race," and (d) the number of respondents in each racial category who are Hispanic or Latino. Investigators may provide the detailed distributions, including all possible combinations, of multiple responses to the racial designations as additional information. However, more detailed items should be designed in a way that they can be aggregated into the required categories for reporting purposes.

For new proposals and clinical research studies begun after January 10, 2002, use the Targeted/Planned Enrollment Table format (MS Word or PDF).

Provide the study title.

The '"Total Planned Enrollment" means the number of subjects that are expected to be enrolled during the entire period of the study and are needed to evaluate the research question The "Total Planned Enrollment" will be reported in two ways in the table: by "Ethnic Category" and by "Racial Categories."

"Ethnic Category": Provide the numeric distribution of the Total Planned Enrollment according to ethnicity and sex/gender in the top part of the table.

"Racial Categories": Provide the numeric distribution of the Total Planned Enrollment, this time by racial categories and sex/gender, in the bottom part of the table. Note that Hispanic is not a racial category.

If there is more than one study/protocol, provide a separate table for each.

List any proposed racial/ethnic subpopulations below the table.

How should I report race and ethnicity data when my research involves a foreign population?

Investigators are encouraged to design their data collection instruments in ways that allow respondent self-identification of their racial and ethnic affiliation. However, these items should be designed in a way that they can be aggregated into the required categories. Also, the investigator can report on any racial/ethnic subpopulations by listing this information in an attachment to the required table. This may be particularly useful when distinctive subpopulations are relevant to the scientific hypotheses being studied.

When completing the tables, investigators should asterisk and footnote the table indicating that data includes foreign participants. If the aggregated data only includes foreign participants, the investigator should provide information in one table with an asterisk and footnote. However, if the study includes both domestic and foreign participants, the investigator should complete two separate tables – one for domestic data and one for foreign data, with an asterisk and footnote accompanying the table with foreign data.

B. Clinical Research Studies begun before January 10, 2002:

If the proposed research uses existing data, then use the formats below for competing continuations and competing supplements. Investigators should review the instructions and Frequently Asked Questions about using the new Enrollment Table format at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html.

Competing Continuations:

For competing continuations involving the collection of new/additional clinical data, use the "Targeted/Planned Enrollment Table (MS Word or PDF)" and the instructions above. *Note:* If you choose to report information with the new Targeted/Planned Enrollment Table, you must continue to use this format for the remaining years of the project.

For competing continuations involving studies begun before January 10, 2002 that do not involve the collection of new/additional clinical data, the data on ethnicity/race and sex/gender may be presented in EITHER the Targeted/Planned Enrollment Table (MS Word or PDF) OR the 4/98 Version of the Inclusion Table (MS Word or PDF). If data were originally collected from study subjects using two questions (one about ethnicity and one about race) and subjects were given the option of selecting more than one race, then use the Targeted/Planned Enrollment Table. Otherwise, use the 4/98 Version of the Inclusion Table, which uses a combined race/ethnicity format with five categories.

Competing Supplements:

For competing supplemental applications involving studies begun before January 10, 2002, investigators may report ethnicity/race and sex/gender composition using EITHER the Inclusion Enrollment Report (MS Word or PDF) OR the 4/98 Version of the Inclusion Table (MS Word or PDF). If data are being collected using two questions (one about ethnicity and one about race) and subjects were given the option of selecting more than one race, then use the Targeted/Planned Enrollment Table. *Note:* If you choose to report information with the new Targeted/Planned Enrollment Table, you must continue to use this format for the remaining years of the project.

If data are being collected using one question that combines ethnicity and race, use the 4/98 Version of the Inclusion Table. For previously funded studies that used the 4/98 Version of the Inclusion Table the earlier reporting format is NOT directly transferable to the format.

C. What Inclusion/Enrollment Table Should Principal Investigators Use for Reporting Accrual Data to NIH? (New versus Old Table)

The following instructions apply to progress reports, whether submitted as part of a non-competing or competing application.

Guidelines for choosing the new Inclusion Enrollment Report Table versus the old Inclusion Table are as follows:

New Inclusion Enrollment Report (MS Word or PDF)

- Studies begun after January 10, 2002, must be designed to ask participants two questions, one about their ethnicity and one about their race, and investigators must use the new Inclusion Enrollment Report table format for reporting summary data to NIH.
- Principal investigators who started a study prior to January 10, 2002 using the old Inclusion Table format for reporting summary data to NIH may switch to the new Inclusion Enrollment Report format if they choose to do so, but they must also change their data collection methods to ask two questions (one about ethnicity and another about race) rather than one question (that combined race and ethnicity) for all participants enrolled in the study from that point on.
- For studies that began prior to January 10, 2002: When the study is submitted for competing continuation and plans to collect new/additional data, the principal investigator is required to change to the new standards for collecting data and use the new Inclusion Enrollment Report format for reporting data to NIH. In some cases, this will mean that principal investigators will need to re-ask study participants about

their race and ethnicity using the new two-question format. Note: principal investigators should not ask again about race and ethnicity if the subjects are no longer participating in the study.

Old Inclusion Table (4/98 Version) MS Word or PDF

- Studies begun prior to January 10, 2002 (and now in their non-competing period) that were structured with one question about race and ethnicity may continue to report enrollment/accrual data to NIH based on the old form, i.e., using five categories of race/ethnicity. However, when they come in for competitive renewal, they will need to change to the new standards/new form for any additional data collection.
- Principal investigators should not switch to the new form if only one question about race and ethnicity is used in data collection.
- Sample of old Inclusion Table format: http://grants.nih.gov/grants/funding/women_min/InclusionOld_Form.pdf

Investigators who have questions about these choices should contact NIH program staff for advice.

Guidance and Additional Instructions

After you have completed the Inclusion of Women and Minorities section, proceed to Inclusion of Children.

INCLUSION OF CHILDREN

- Create a section entitled “Inclusion of Children” and place it immediately following the last entry in the Inclusion of Women and Minorities section.
- For the purpose of implementing these guidelines, a *child* is defined as an individual under the age of 21 years (for additional information see http://grants.nih.gov/grants/funding/children/children.htm and http://grants.nih.gov/grants/guide/notice-files/not98-024.html).
- Provide either a description of the plans to include children or, if children will be excluded from the proposed research, application, or proposal, then you must present an acceptable justification (see below) for the exclusion.
- If children are included, the description of the plan should include a rationale for selecting a specific age range of children. The plan also must include a description of the expertise of the investigative team for dealing with children at the ages included, of the appropriateness of the available facilities to accommodate the children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.
- Scientific Review Groups will assess each proposal as being "acceptable" or "unacceptable" with regard to the age-appropriate inclusion or exclusion of children in the research project.
- When children are involved in research, the Additional Protections for Children Involved as Subjects in Research (45 C.F.R. 46 Subpart D) apply and must be addressed in the “Human Subjects Research and Protection from Risks” subheading.

Justifications for Exclusion of Children

For the purposes of this policy, all individuals under 21 are considered children; however, exclusion of any specific age group, such as individuals under 18, should be justified in this section.

It is expected that children will be included in all clinical research unless one or more of the following exclusionary circumstances can be fully justified:

1. The research topic to be studied is not relevant to children.
2. There are laws or regulations barring the inclusion of children in the research.
3. The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be needlessly redundant. Documentation of other studies justifying the exclusions should be provided. NIH program staff can be contacted for guidance on this issue if the information is not readily available.
4. A separate, age-specific study in children is warranted and preferable. Examples include:
   a. The condition is relatively rare in children, as compared to adults (in that extraordinary effort would be needed to include children, although in rare diseases or disorders where the applicant has made a particular effort to assemble an adult population, the same effort would be expected to assemble a similar child population with the rare condition); or
   b. The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network; or
   c. Issues of study design preclude direct applicability of hypotheses and/or interventions to both adults and children (including different cognitive, developmental, or disease stages or different age-related metabolic processes). While this situation may represent a justification for excluding children in some instances, consideration should be given to taking these differences into account in the study design and

expanding the hypotheses tested, or the interventions planned, to allow inclusion of children rather than excluding them.

5. Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). Although children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis.
6. Study designs are aimed at collecting additional data on pre-enrolled adult study subjects (e.g., longitudinal follow-up studies that did not include data on children).
7. Other special cases can be justified by the investigator and found acceptable to the review group and the Institute Director.

Guidance and Additional Instructions

See Policy on Inclusion of Children.

SCENARIO A: NO HUMAN SUBJECTS RESEARCH PROPOSED

Criterion:

If you are uncertain as to whether your research involves Human Subjects please read: Question 1: Does your proposed research involve human subjects?

Instructions:

Check the box marked “No” on the Proposal Cover Sheet (Appendix A) and indicate “No” on the “Proposal Summary and Data Record (Appendix G).

In your proposal narrative, create a heading labeled “E. Human Subjects Research” and place it immediately after the last entry in the Research Design and Methods section. Include the following statement below the heading: “No Human Subjects Research is proposed in this proposal.”

If your proposed research involves human specimens and/or data from subjects, please provide a justification for your claim that no human subjects are involved (see guidance under Question 1: Does your proposed research involves human subjects?).

Guidance and Additional Instructions

The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research.

Do not follow the instructions for Scenario A if research activities involving human subjects are planned at any time during the proposed project period, either at the applicant organization or at any other performance site or collaborating institution. You will need to consider an alternative scenario.

If you need to consider an alternative scenario return to the Decision Table.

SCENARIO B: HUMAN SUBJECTS RESEARCH CLAIMING EXEMPTION 4

Criteria:

Human Subjects Research	Yes
Exemption	4
Clinical Research	No
Clinical Trial	N/A
NIH-Defined Phase III Clinical Trial	N/A

Instructions and Required Information:

Although no specific page limitation applies to this section of the proposal, be succinct in your responses.

Check the box marked "Yes" on the Proposal Cover Sheet (Appendix A). Indicate "Yes" on the Proposal Summary and Data Record and insert E-4 in the field for Exemption Number (Appendix G). Check "Yes" if activities involving human subjects are planned at any time during the proposed project period, either at the applicant organization or at any other performance site or collaborating institution. "Yes" should be checked even if the research is exempt from requirements in the Federal regulations for the protection of human subjects (45 C.F.R. 46).

In your proposal narrative, create a heading entitled "E. Human Subjects Research" and place it immediately after the last entry in the Research Design and Methods section. Include the following statement below the heading: "This Human Subjects Research falls under Exemption 4."

Address the following three items in this new section:

1. Human Subjects Involvement and Characteristics:

a. Describe the proposed involvement of human subjects in the work outlined in the Research Design and Methods section.

b. Describe the characteristics of the subject population, including their anticipated number, age range, and health status. If the characteristics of the population are not available, then the applicant should indicate that the information is unknown.

c. Identify the criteria for inclusion or exclusion of any subpopulation.

d. Explain the rationale for the involvement of vulnerable populations, such as fetuses, neonates, pregnant women, children, institutionalized individuals, or others who may be considered vulnerable populations. Exemptions 1-6 do not apply to research involving prisoners or subjects who become prisoners (see 45 C.F.R. Part 46 Subpart C). Although Exemptions 1 and 3-6 apply to research involving children (see 45 C.F.R. Part 46 Subpart D), Exemption 2 can only be used for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

e. List any collaborating sites where human subjects research will be performed and describe the role of those sites in performing the proposed research.

2. Sources of Materials:

a. Describe the research material obtained from living human subjects in the form of specimens, records, or data.

b. Describe any data that will be recorded on the human subjects involved in the project.

c. Describe the linkages to subjects, and indicate who will have access to subject identities.

d. Provide information about when the specimens, records, or data were collected and whether new material or data will need to be collected specifically for your proposed research project.

3. Justification for Exemption:

a. Indicate that you are claiming Exemption 4.

b. Provide a justification for why your research meets the criteria for Exemption 4.

Guidance and Additional Instructions

The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research.

What types of research meet the criteria for Exemption 4? Research projects involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. Determining the appropriateness of Exemption 4 for research using specimens and data can be complex.

Note: Prospective collection of additional specimens does not meet the criteria for Exemption 4.

If you are uncertain as to whether your research meets the criteria for Exemption 4, refer to Exemption 4 Guidance and Information.

If you need to consider an alternative scenario, return to the Decision Table.

SCENARIO C: HUMAN SUBJECTS RESEARCH CLAIMING EXEMPTION 1,2,3,5, OR 6

Criteria:

Human Subjects Research	Yes
Exemption Claimed	1, 2, 3, 5, 6
Clinical Research	Yes
Clinical Trial	N/A
NIH-Defined Phase III Clinical Trial	N/A

Instructions and Required Information:

Although no specific page limitation applies to this section of the proposal, be succinct.

Check the box marked “Yes” on the Proposal Cover Sheet (Appendix A). Indicate “Yes” on the Proposal Summary and Data Record and insert E-1, E-2, E-3, E-5, or E-6, as appropriate, in the field for Exemption Number (Appendix G).

Although your research may be exempt from the IRB oversight provisions, it is still human subjects research, and you need to follow the instructions that are identified for each of the following topics and provide the information that is requested.

In your proposal narrative, create a heading entitled “E. Human Subjects Research” and place it immediately after the last entry in the Research Design and Methods section. Address the following items in this new section. Include the following statement below the heading: “This Human Subjects Research falls under Exemption(s) … .”

1. Human Subjects Involvement and Characteristics:

a. Describe the proposed involvement of human subjects in the work outlined in the Research Design and Methods section.

b. Describe the characteristics of the subject population, including their anticipated number, age range, and health status.

c. Identify the criteria for inclusion or exclusion of any subpopulation (e.g., men, women, children).

d. Explain the rationale for the involvement of vulnerable populations, such as fetuses, neonates, pregnant women, children, institutionalized individuals. Please note that research involving prisoners is not exempt under any category (see 45 C.F.R. 46 Subpart C).

e. List any collaborating sites where human subjects research will be performed and describe the role of those sites in performing the proposed research.

2. Sources of Materials:

a. Describe the sources of the research material obtained from living human subjects in the form of specimens, records, or data.

b. Describe any data that will be recorded on the human subjects involved in the project.

c. Describe the linkages to subjects and indicate who will have access to subject identities.

d. Provide information about when the specimens, records, or data were collected and whether new material or data will need to be collected specifically for your proposed research project.

3. Justification for Exemption(s)

In this section, identify which exemption(s) (1, 2, 3, 5, or 6) you are claiming. (If you are claiming Exemption 4 please refer to Scenario B and the appropriate instructions.) Justify why your research is appropriate for the exemption(s) that you have claimed.

4. Inclusion of Women and Minorities (click and follow instructions)

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the scientific objectives of the study.

Create a section entitled “Inclusion of Women and Minorities” and place it immediately following the last entry in the “Human Subjects Research” section.

Describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan should contain a description of the proposed outreach programs for recruiting women and minorities as participants. See http://grants.nih.gov/grants/funding/women_min/women_min.htm.

Include the Targeted/Planned Enrollment Table (MS Word or PDF) here.

5. Inclusion of Children (click and follow instructions)

For the purpose of implementing these guidelines, a child is defined as an individual under the age of 21 years. (For additional information see http://grants.nih.gov/grants/funding/children/children.htm and http://grants.nih.gov/grants/guide/notice-files/not98-024.html.)

Guidance and Additional Instructions

The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research.

If you are uncertain as to whether your research meets the criteria for an exemption please read: Question 2: Does your proposed human subjects research meet the criteria for one or more of the exemptions in the HHS regulations?

If you need to consider an alternative Scenario, return to the Decision Table.

SCENARIO D: CLINICAL RESEARCH

Criteria

Human Subjects Research	Yes
Exemption	No
Clinical Research	Yes
Clinical Trial	No
NIH-Defined Phase III Clinical Trial	No

Instructions and Required Information:

Although no specific page limitation applies to this section of the proposal, be succinct.

Check the box marked “Yes” on the Proposal Cover Sheet (Appendix A) and indicate “Yes” on the Proposal Summary and Data Record (Appendix G).

In your proposal narrative, create a section entitled “E. Human Subjects Research” immediately following the last entry in the Research Design and Methods section. Include the following statement below the heading: “This Human Subjects Research meets the definition of ‘Clinical Research.’”

Create a subheading for each of the following items, follow the instructions that are identified for each topic, and provide the information that is requested:

- ***Protection of Human Subjects*** (click and follow instructions)
- ***Inclusion of Women and Minorities*** (click and follow instructions)
  Targeted/Planned Enrollment Table (MS Word or PDF)
- ***Inclusion of Children*** (click and follow instructions)

If your proposal involves collaborating sites, provide the information identified above for each participating site.

Guidance and Additional Instructions

Research that meets the criteria for Exemption 4 is not considered clinical research.

Research that uses *existing (archived)* specimens or data that *can* be linked to living individuals must address the inclusion of women, minorities and children as identified above, unless the investigator does not have access to the information. The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research.

If you are uncertain as to whether your research meets the criteria for clinical research, read: Question 3: Does your proposed research meet the definition of Clinical Research?

If you need to consider an alternative scenario, return to the Decision Table.

SCENARIO E. CLINICAL TRIALS

Criteria

Human Subjects Research	Yes
Exemption	No
Clinical Research	Yes
Clinical Trial	Yes
NIH-Defined Phase III Clinical Trial	No

Instructions and Required Information:

Check the box marked "Yes" on the Proposal Cover Sheet (Appendix A) and indicate "Yes" on the Proposal Summary and Data Record (Appendix G). In addition, complete the items regarding the Institution's General Assurance, Institution's Review Board, informed consent and clinical protocol.

In your proposal narrative, create a section entitled "E. Human Subjects Research" immediately following the last entry in the Research Design and Methods section. Include the following statement below the heading: "This Human Subjects Research meets the definition of a clinical trial." Create a subheading for each of the following items, follow the instructions that are identified for each topic, and provide the information that is requested:

- ***Protection of Human Subjects*** (click and follow instructions).Include the statement "This Human Subjects Research meets the definition of Clinical Research" after the heading.
- ***Data and Safety Monitoring Plan*** (click and follow instructions)
- ***Inclusion of Women and Minorities*** (click and follow instructions)
  Targeted/Planned Enrollment Table (MS Word or PDF)
- ***Inclusion of Children*** (click and follow instructions)

If your proposal involves collaborating sites, provide information for each of the issues identified above for each participating site.

Guidance and Additional Instructions

The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research. If you are uncertain as to whether your research includes a clinical trial please read: Question 4: Does your proposed research include a clinical trial? If you need to consider an alternative scenario, return to the Decision Table.

SCENARIO F. NIH-DEFINED PHASE III CLINICAL TRIAL

Criteria

Human Subjects Research:	Yes
Exempt:	No
Clinical Research:	Yes
Clinical Trial:	Yes
NIH-Defined Phase III Clinical Trial:	Yes

Instructions and Required Information:

Check the box marked "Yes" on the Proposal Cover Sheet (Appendix A) and indicate "Yes" on the Proposal Summary and Data Record (Appendix G). In addition, complete the items regarding the Institution's General Assurance, Institution's Review Board, informed consent and clinical protocol.

In your proposal narrative, create a section entitled "E. Human Subjects Research" immediately following the last entry in the Research Design and Methods section. Include the following statement below the heading: "This Human Subjects Research is an NIH-Defined Phase III Clinical Trial."

Follow the instructions that are identified for each of the following topics and provide the information that is requested:

- ***Protection of Human Subjects*** (click and follow instructions)
- ***Data and Safety Monitoring Plan*** (click and follow instructions)
- ***Inclusion of Women and Minorities*** (click and follow instructions)
  Targeted/Planned Enrollment Table (MS Word or PDF)
- ***Inclusion of Children*** (click and follow instructions)

If your proposal involves collaborating sites, provide the information identified above for each participating site.

Guidance and Additional Instructions

The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research. If you are uncertain as to whether your research includes clinical research, read Question 5: Does your proposed research meet criteria for an NIH-Defined Phase III Clinical Trial?

If you need to consider an alternative scenario, return to the Decision Table.

HUMAN SUBJECTS RESEARCH POLICY

Human Subjects Research Policy includes federal regulations for the protection of human subjects and the following NIH policies related to human subjects research.

PROTECTION OF HUMAN SUBJECTS

The Department of Health and Human Services (HHS) regulations for the protection of human subjects provide a systematic means, based on established, internationally recognized ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the HHS. The regulations stipulate that an applicant organization, whether domestic or foreign, bears responsibility for safeguarding the rights and welfare of human subjects in HHS-supported research activities. The regulations require that applicant organizations proposing to involve human subjects in nonexempt research, provide written Assurance of Compliance with the Office for Human Research Protections (OHRP), that they will comply with requirements set forth in the HHS regulations to protect human subjects. These regulations, 45 C.F.R. 46, Protection of Human Subjects, are available from OHRP, Department of Health and Human Services, The Tower Building, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852 or by contacting OHRP at ohrp@osophs.dhhs.gov, Telephone: 1-866-447-4777 or (301) 496-7005.

Under HHS regulations to protect human subjects from research risks, certain research areas are exempt. However, if an applicant makes inappropriate designations of the noninvolvement of human subjects or of exempt categories of research, this may result in delays in the review of a proposal or the return of the proposal without review. The PHS will make a final determination as to whether the proposed activities are covered by the regulations or are in an exempt category, based on the information provided in the Research Plan. When in doubt, consult with the Office for Human Research Protections (OHRP), Department of Health and Human Services by accessing their website http://www.hhs.gov/ohrp for guidance and further information.

No non-exempt research involving human subjects can be conducted under a HHS award unless that organization is operating in accord with an approved Assurance of Compliance and provides verification that an Institutional Review Board (IRB) that is registered under the specific Assurance has reviewed and approved the proposed activity in accordance with the HHS regulations. No award to an individual will be made unless that individual is affiliated with an assured organization that accepts responsibility for compliance with the HHS regulations. Foreign applicant organizations must also comply with the provisions of the regulations.

In addition to the HHS human subjects regulations, FDA regulations (21 C.F.R. part 50; 21 C.F.R. part 56) may also apply to your research. FDA regulations generally apply to biomedical research involving an unapproved drug, device or biologic and may apply to certain studies of approved products. Researchers proposing such research should consult with their IRB and the FDA to determine whether and how the FDA regulations may apply. Additional information on FDA regulations is available at (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm).

Studies that involve the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into human research participants (known as “human gene transfer” or “gene therapy”) are subject to the oversight and biosafety requirements outlined in the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines) when these studies are conducted at, or sponsored by, an institution that receives any NIH support for recombinant DNA research. These requirements, which include review by an Institutional Biosafety Committee and submission to the NIH for review by the Recombinant DNA Advisory Committee, are described in Section III-C-1 and Appendix M of the NIH Guidelines (accessible at: http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html). Additional information on the special requirements that pertain to human gene transfer can be found in a series of Frequently Asked Questions at: http://www4.od.nih.gov/oba/RAC/RAC_FAQs.htm.

Federal requirements to protect human subjects apply to most research on human specimens (such as cells, blood, and urine), residual diagnostic specimens and medical information. Research involving the collection or study of existing data, documents, records, pathological specimens, diagnostic specimens, or tissues that are individually identifiable is considered “research involving human subjects.” The NIH Office of Extramural Research Human Subjects website contains additional information and Frequently Asked Questions that is available to help

investigators understand how these federal requirements apply to their research. See http://grants.nih.gov/grants/policy/hs/index.htm.

The HHS regulations also require "Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency" (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.120). This independent evaluation is conducted at the NIH through the peer review system and NIH staff review, and, as required, will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. On the basis of this evaluation, the NIH may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

VULNERABLE POPULATIONS

Investigators who conduct research involving pregnant women, human fetuses and neonates, prisoners, or children must follow the provisions of the regulations in Subparts B, C, and D of 45 C.F.R. Part 46, respectively, which describe the additional protections required for these populations. Note that 'prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers) as well as subjects who become incarcerated after the study begins. Relevant information may be obtained at the OHRP website (http://www.hhs.gov/ohrp/policy/index.html).

REMINDER: HHS regulations at 45 C.F.R. Part 46, subpart C describe requirements for additional protections for research involving prisoners as subjects *or* individuals who become prisoners after the research has started. Refer to: http://www.hhs.gov/ohrp/humansubjects/guidance/prisoner.htm for complete instructions.

Exemptions 1-6 do not apply to research involving prisoners or subjects who become prisoners (see Subpart C). Although Exemptions 1 and 3-6 apply to research involving children (see Subpart D), Exemption 2 can only be used for educational tests or research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

DATA AND SAFETY MONITORING PLANS FOR CLINICAL TRIALS

For each proposed clinical trial, NIH requires a data and safety monitoring plan that describes oversight and monitoring to ensure the safety of participants and the validity and integrity of the data. The level of monitoring should be commensurate with the risks and the size and complexity of the clinical trial. A detailed data and safety monitoring plan must be submitted to the applicant's IRB and subsequently to the funding IC for approval prior to the accrual of human subjects. The reporting of Adverse Events must be reported to the IRB, the NIH funding Institute or Center, and other required entities. This policy requirement is in addition to any monitoring requirements imposed by 45 C.F.R. Part 46. NIH requires the establishment of a Data and Safety Monitoring Board (DSMB) for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase III clinical trials.

RESEARCH ON TRANSPLANTATION OF HUMAN FETAL TISSUE

In signing the Proposal Cover Page, the duly authorized representative of the applicant organization certifies that if research on the transplantation of human fetal tissue is conducted, the applicant organization will make available, for audit by the Secretary, HHS, the physician statements and informed consents required by section 498A (b)(2) and (c) of the Public Health Service Act, 42 U.S.C. 289g (b)(2) and (c), or ensure HHS access to those records, if maintained by an entity other than the applicant organization.

RESEARCH USING HUMAN EMBRYONIC STEM CELLS

http://stemcells.nih.gov/index.asp

In signing the Proposal Cover Page, the duly authorized representative of the applicant organization certifies that if research using human embryonic stem cells is proposed, the applicant organization will be in compliance with the "Notice of Extended Receipt Date and Supplemental Information Guidance for Applications Requesting

Funding that Proposes Research with Human Embryonic Stem Cells" (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-006.html).

IRB APPROVAL

NIH does not require certification of IRB approval of the proposed research prior to NIH peer review of an application. See http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-031.html.

Following NIH peer review, applicants and their institutions will be notified of the need for review and approval of the proposed research by an OHRP-registered IRB. See http://www.hhs.gov/ohrp to register an IRB. Documentation of IRB approval must be sent to the Grants Management Office identified in the notice requesting certification. This IRB certification must include: the PHS application number, title of the project, name of the principal investigator/program director, date of IRB approval, and appropriate signatures. You may also use the optional form "Protection of Human Subjects - Assurance Identification/IRB Certification/Declaration of Exemption (Common Rule) (OMB Form No. 0990-0263) to meet this requirement: http://www.hhs.gov/ohrp/humansubjects/assurance/OF310.rtf

An institution is automatically considered to be engaged in human subjects research when it receives an NIH award to support nonexempt human subjects research. All institutions engaged in human subjects research must obtain a Federal Wide Assurance (FWA) from OHRP. Instructions for applying for a Federal Wide Assurance (FWA) are available from the OHRP website at http://www.hhs.gov/ohrp/assurances/assurances_index.html.

Any modifications in the Research Plan section of the proposal, required by either NIH or by the IRB must be submitted with the follow-up certification of IRB approval to the NIH before the competing award is made. It is the responsibility of the principal investigator/program director and the applicant organization to submit the follow-up certification.

If more than year will have elapsed between the initial IRB review date and the anticipated award date, the awarding unit staff shall require re-review by the IRB prior to award.

REQUIRED EDUCATION IN THE PROTECTION OF HUMAN RESEARCH PARTICIPANTS

NIH requires education on the protection of human research participants for all individuals identified as Key Personnel before funds are awarded for applications or contract proposals involving human subjects. For information relating to this requirement, see the following see the following notices (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html and http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html), and Frequently Asked Questions found at: http://grants.nih.gov/grants/policy/hs_educ_faq.htm. Prior to award, applicants will be required to provide a description of education completed in the protection of human subjects for all Key Personnel involved in human subjects research. Although NIH does not endorse programs, there are curricula available that can provide guidance or that can be modified to provide training in this area. See http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp for computer-based training developed for NIH that can be downloaded at no charge. For information on facilitating education and developing curricula, see http://www.nih.gov/sigs/bioethics.

RELEVANT POLICIES AND INFORMATION

PROCEDURES FOR SUBMISSION OF COMPLIANCE DOCUMENTS TO THE HUMAN PLURIPOTENT STEM CELL REVIEW GROUP FOR THE RESEARCH USE OF HUMAN EMBRYONIC GERM CELLS	NOTICE: NOT-OD-02-049 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-049.html
GUIDANCE FOR INVESTIGATORS AND INSTITUTIONAL REVIEW BOARDS REGARDING RESEARCH INVOLVING HUMAN EMBRYONIC STEM CELLS, GERM CELLS AND STEM CELL-DERIVED TEST ARTICLES	NOTICE: NOT-OD-02-044 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-044.html

IMPLEMENTATION ISSUES FOR HUMAN EMBRYONIC STEM CELL RESEARCH - FREQUENTLY ASKED QUESTIONS	NOTICE: NOT-OD-02-014 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-014.html
FEDERAL GOVERNMENT CLEARANCES FOR RECEIPT OF INTERNATIONAL SHIPMENT OF HUMAN EMBRYONIC STEM CELLS	NOTICE: NOT-OD-02-013 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-013.html
NOTICE OF EXTENDED RECEIPT DATE AND SUPPLEMENTAL INFORMATION GUIDANCE FOR APPLICATIONS REQUESTING FUNDING THAT PROPOSES RESEARCH WITH HUMAN EMBRYONIC STEM CELLS	NOTICE: NOT-OD-02-006 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-006.html
NOTICE OF CRITERIA FOR FEDERAL FUNDING OF RESEARCH ON EXISTING HUMAN EMBRYONIC STEM CELLS AND ESTABLISHMENT OF NIH HUMAN EMBRYONIC STEM CELL REGISTRY	NOTICE: NOT-OD-02-005 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html
NIH FUNDING OF RESEARCH USING SPECIFIED EXISTING HUMAN EMBRYONIC STEM CELLS	NOTICE: NOT-OD-01-058 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-059.html

NIH POLICY ON THE INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH

It is the policy of NIH that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made by the Director, NIH, upon the recommendation of an Institute/Center Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. All NIH-supported biomedical and behavioral research involving human subjects is defined as clinical research. This policy applies to research subjects of all ages.

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the scientific objectives of the study. The research plan should describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan should contain a description of the proposed outreach programs for recruiting women and minorities as participants. See http://grants.nih.gov/grants/funding/women_min/women_min.htm.

NIH POLICY ON INCLUSION OF CHILDREN

(See Definition of "child.")

Research involving children must comply with the NIH Policy and Guidelines on the Inclusion of Children in Clinical Research. The following excerpts provide the key policy statements. Investigators should obtain full copies of the Policy and Guidelines from NIH staff, or from the NIH grants Web site under http://grants.nih.gov/grants/funding/children/children.htm.

NIH policy requires that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH unless there are clear and compelling reasons not to include them. Therefore, proposals for clinical research must include a description of plans for including children. If children will be excluded from the research, the proposal or proposal must present an acceptable justification for the exclusion.

In addition, the involvement of children as subjects in research must be in compliance with all applicable subparts of 45 C.F.R. Part 46 as well as with other pertinent Federal laws and regulations.

Additionally, IRBs have special review requirements to protect the well-being of children who participate in research. These requirements relate to risk, benefit, parental/guardian consent, and assent by children, and to research involving children who are wards of the state or of another institution. The local IRB approves research that satisfies the conditions set forth in the regulations.

NIH POLICY ON REPORTING RACE AND ETHNICITY DATA: SUBJECTS IN CLINICAL RESEARCH

The Office of Management and Budget (OMB) (http://www.whitehouse.gov/omb/fedreg/ombdir15.html) defines minimum standards for maintaining, collecting and presenting data on race and ethnicity for all Federal reporting agencies (including NIH). The categories in this classification are social-political constructs and should not be interpreted as being anthropological in nature. The standards were revised in 1997 and now include two ethnic categories, "Hispanic or Latino" and "Not Hispanic or Latino." There are five racial categories: American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; and White. Reports of data on race and ethnicity shall use these categories. NIH is required to use these definitions to allow comparisons to other federal databases, especially the census and national health databases. The following definitions apply to the minimum standards for the ethnic and racial categories.

Ethnic Categories:

Hispanic or Latino: A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term, “Spanish origin,” can be used in addition to “Hispanic or Latino.”

Not Hispanic or Latino

Racial Categories:

American Indian or Alaska Native: A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or community attachment.

Asian: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American: A person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

Native Hawaiian or Other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White: A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Ethnic/Racial Subpopulations: In addition to OMB ethnic and racial categories, NIH uses the following definition for ethnic/racial subpopulations:

Subpopulations: Each ethnic/racial group contains subpopulations that are delimited by geographic origins, national origins, and/or cultural differences. It is recognized that there are different ways of defining and reporting racial and ethnic subpopulation data. The subpopulation to which an individual is assigned depends on self-reporting of specific origins and/or cultural heritage. Attention to subpopulations also applies to individuals who self identify with more than one race. These ethnic/racial combinations may have biomedical, behavioral, and/or social-cultural implications related to the scientific question under study. (http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm)

GUIDANCE ON COLLECTING RACE AND ETHNICITY DATA FROM STUDY SUBJECTS

When an investigator is planning to collect data on ethnicity and race, the categories identified above should be used. The collection of greater detail is encouraged, for example on ethnic/racial subpopulations. However, any collection that uses more detail must be designed in a way that data can be aggregated into these minimally required categories. Use self-report or self-identification to collect this information by asking two separate

questions – one on ethnicity and one on race. Collect ethnicity information first followed by the question on race and provide subjects with the option to select more than one racial category. An example of a format for collecting information from study subjects in the US and that meets the OMB requirements can be found in the Ethnic Origin and Race section of the Personal Data Form Page (MS Word or PDF) in the PHS 398.

See NIH Policy on Inclusion of Women and Minorities.

Collecting Data on Foreign Populations: If you are conducting clinical research outside of the US, you should design culturally sensitive and appropriate data collection items and instruments that allow subjects to self-identify their ethnic and racial affiliation in a culturally appropriate manner. These items, however, should be designed in a way that allow you, the investigator, to aggregate the information into the OMB minimally required ethnic and racial categories when reporting the information to NIH.

Submitting Applications or Proposals Using Existing Data in Clinical Research with No Plans for Collecting New/Additional Data:

Investigators are instructed to provide plans for the total number of subjects proposed for the study and to provide the distribution by ethnic/racial categories and sex/gender. Under these circumstances, investigators are not required to re-contact subjects solely to comply with the newly revised categories. If the existing data on ethnicity and race allow accurate correspondence with the new categories, the investigator can use the format in the Targeted/Planned Enrollment table (MS Word or PDF). However, if the existing data do not allow accurate correspondence with the new categories, information may be reported using the former categories and according to the format in the 4/98 Version of the Inclusion Table
http://grants.nih.gov/grants/funding/women_min/InclusionOld_Form.pdf

Annual Progress Reports (Type 5 applications) and Competing Supplement Applications

In annual Progress Reports, investigators conducting clinical research are required to provide the cumulative total enrollment of subjects to-date, showing the distribution by ethnic/racial categories and sex/gender on EITHER the new Inclusion Enrollment Report (MS Word or PDF) OR the format in the former 4/98 Version of the Inclusion Table (MS Word or PDF).

For competing supplement applications, any proposed additions to the Targeted/Planned Enrollment Table should be provided, in addition to the current Inclusion Enrollment Table.

If Data Collection is Ongoing, Such that New Subjects Will be Enrolled and/or Additional Data Will be Collected from Human Subjects:

Investigators may choose to report ethnicity/race and sex/gender sample composition using EITHER the new Inclusion Enrollment Report (MS Word or PDF) OR the format in the former 4/98 Version of the Inclusion Table (MS Word or PDF).

[Note: If investigators with on-going data collection choose to report information using the new Inclusion Enrollment Report, they must continue to use this format for the remaining years of the project.]

If Data Collection is Complete, Such that No New/Additional Subject Contact is Planned:

Investigators may EITHER continue to report using the former categories and according to the 4/98 Version of the Inclusion Table, OR, if data allow accurate correspondence with the new categories, use the format in the new Inclusion Enrollment Report.

Additional Information

Additional information on NIH policy regarding the Inclusion of Women and Minorities in Clinical Research can be found at the website http://grants.nih.gov/grants/funding/women_min/women_min.htm.

HUMAN SUBJECTS RESEARCH DEFINITIONS

Autopsy Materials. The use of autopsy materials is governed by applicable Federal, state and local law and is not directly regulated by 45 CFR Part 46.

Child. The NIH Policy on Inclusion of Children defines a child as an individual under the age of 21 years. The intent of the NIH policy is to provide the opportunity for children to participate in research studies when there is a sound scientific rationale for including them, and their participation benefits children and is appropriate under existing Federal guidelines. Thus, children must be included in NIH conducted or supported clinical research unless there are scientific and ethical reasons not to include them.

HHS Regulations (45 CFR Part 46, Subpart D, Sec.401-409) provide additional protections for children involved as subjects in research, based on this definition: “Children are persons who have not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted.” Generally, state laws define what constitutes a “child.” Consequently, the age at which a child's own consent is required and sufficient to participate in research will vary according to state law. For example, some states consider a person age 18 to be an adult and therefore one who can provide consent without parental permission.

Clinical Research. NIH defines human clinical research as: (1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are *in vitro* studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies. (2) Epidemiologic and behavioral studies. (3) Outcomes research and health services research. Note: Studies falling under Exemption 4 for human subjects research are not considered clinical research by this definition.

Clinical Trial. The NIH defines a *clinical trial* as a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective.

Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits this definition of a clinical trial.

Human subjects research to develop or evaluate clinical laboratory tests (e.g. imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test will be used for medical decision making for the subject or the test itself imposes more than minimal risk for subjects.

Biomedical clinical trials of experimental drug, treatment, device or behavioral intervention may proceed through four phases:

> ***Phase I*** clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects).
>
> ***Phase II*** clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.
>
> ***Phase III*** studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.

Phase IV studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

NIH-Defined Phase III Clinical Trial. For the purpose of the Guidelines an NIH-defined Phase III clinical trial is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

Data and Safety Monitoring Plan. NIH requires a data and safety monitoring plan for each clinical trial that will provide oversight and monitoring to ensure the safety of participants and the validity and integrity of the data. The level of monitoring should be commensurate with the risks and the size and complexity of the clinical trial. A detailed data and safety monitoring plan must be submitted to the applicant's IRB and subsequently to the funding IC for approval prior to the accrual of human subjects. The reporting of Adverse Events must be reported to the IRB, the NIH funding Institute or Center, and other required entities. This policy requirement is in addition to any monitoring requirements imposed by 45 CFR Part 46.

Data and Safety Monitoring Board (DSMB). NIH requires the establishment of a Data and Safety Monitoring Board (DSMB) for multi-site clinical trials involving interventions that entail potential risk to the participants, *and generally for Phase III clinical trials*.

Gender. Refers to the classification of research subjects into either or both of two categories: women and men. In some cases, representation is unknown, because gender composition cannot be accurately determined (e.g., pooled blood samples or stored specimens without gender designation).

Human Subjects. The HHS regulations "Protection of Human Subjects" (45 CFR 46, administered by OHRP) define a ***human subject*** as a living individual about whom an *investigator* conducting *research obtains*:

- data through *intervention* or *interaction* with the individual or
- *identifiable private information*

Investigator. The OHRP considers the term investigator to include anyone involved in conducting the research. OHRP does not consider the act of solely providing coded private information or specimens (for example, by a tissue repository) to constitute involvement in the conduct of the research. However, if the individuals who provide *coded* information or specimens also collaborate on other activities related to the conduct of the research with the investigators who receive such information or specimens, they will be considered to be involved in the conduct of the research. [OHRP's Coded Specimen Guidance]

Research. HHS regulations define *research* at 45 CFR 46.102(d) as follows:
Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

Obtains. In its guidance for use of coded specimens, OHRP has determined that under the definition of human subject at 45 CFR 46.102(f), *obtaining* identifiable private information or identifiable specimens for research purposes constitutes human subjects research. *Obtaining* means receiving or accessing identifiable private information or identifiable specimens for research purposes. OHRP interprets *obtaining* to include an investigator's use, study, or analysis for research purposes of *identifiable private information* or identifiable specimens already in the possession of the investigator.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. (45 CFR 46.102(f))

Interaction includes communication or interpersonal contact between investigator and subject. (45 CFR 46.102(f))

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record). Private information must be *individually identifiable* (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. (45 CFR 46.102(f))

Individually Identifiable Private Information. According to its guidance for use of coded specimens, OHRP generally considers private information or specimens to be *individually identifiable* as defined at 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through *coding* systems. Conversely, OHRP considers private information or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Coded. With respect to private information or human biological specimens, *coded* means that:

(1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol or combination thereof (i.e., the code); and

(2) a key to decipher the code exists, enabling linkage of the identifying information with the private information or specimens.

Research that involves only coded private information/data or coded human biological specimens may not constitute human subjects research under the HHS human subjects regulations (45 CFR 46) if:

- the specimens and/or information/data are not obtained from an interaction/intervention with the subject specifically for the research; and
- the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain (e.g., the researcher's access to subject identities is prohibited).

  (See the following guidance from the Office for Human Research Protections (OHRP) for additional information and examples: http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf.)

Significant Difference. For purposes of NIH policy, a “significant difference” is a difference that is of clinical or public health importance, based on substantial scientific data. This definition differs from the commonly used “statistically significant difference,” which refers to the event that, for a given set of data, the statistical test for a difference between the effects in two groups achieves statistical significance. Statistical significance depends upon the amount of information in the data set. With a very large amount of information, one could find a statistically significant, but clinically small difference that is of very little clinical importance. Conversely, with less information one could find a large difference of potential importance that is not statistically significant.